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BioTime to Receive \$43 Million From Juvenescence

Published: Aug 02, 2018

ALAMEDA, Calif.--(BUSINESS WIRE)-- BioTime, Inc. (NYSE American: BTX), a clinical-stage biotechnology company focused on degenerative diseases, today announced a new strategic alignment between AgeX Therapeutics and Juvenescence Limited, a global leader in developing therapeutics focused on improving and extending human lifespans.

Under the terms of the agreement, Juvenescence will purchase, in a single transaction, 14.4 million shares of AgeX Therapeutics from BioTime for \$43.2 million. 50% of the purchase price will be paid to BioTime in cash and the remaining 50% will be a 2-year convertible/redeemable note with an annual interest rate of 7%, payable at maturity.

Antoxerene Closes \$10 Million Deal with Juvenescence to Develop Small Molecule Drugs for Diseases of Aging

July 12, 2018 10:50 AM Eastern Daylight Time

LAFAYETTE, N.Y.--(BUSINESS WIRE)--Antoxerene, Inc., a portfolio company of Ichor Therapeutics, Inc., focused on small molecule drug discovery for pathways of aging, announced today the launch of a joint venture with Juvenescence Limited. The joint venture, called FoxBio, Inc., will develop Antoxerene's collection of small molecules that target senescent cells. Juvenescence will support the venture with \$10 million in equity financing and drug development expertise.

“There has been a lot of interest surrounding the therapeutic applications of senolytic drugs – compounds that clear toxic senescent cells – particularly with respect to age-associated disease”

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“There has been a lot of interest surrounding the therapeutic applications of senolytic drugs – compounds that clear toxic senescent cells – particularly with respect to age-associated disease” said Kelsey Moody, CEO at Antoxerene. “As molecular pathways unique to senescent cells have begun to be identified, we can now develop drugs to target these pathways. We are eager to work with the Juvenescence team, whose experience in drug development, technical depth, and visionary leadership will help us to deliver on the immense potential of this field.”

AUGUST 1, 2018 BY ADMIN

Ichor announces \$1M life science strategic fund in Syracuse

LAFAYETTE, NY: Today, Ichor Therapeutics, a biotechnology company that develops therapeutic interventions for age-associated disease, announced the formation of Grapeseed.Bio, a life science strategic fund and accelerator program.

Through this program, life science entrepreneurs receive up to \$100k in seed funding, technical training, full access to Ichor's research laboratory, and mentorship in exchange for equity.



It is necessary to establish an International Agency for Research on Aging

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How to Cite

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Abstract

The global aging of human population is one of the main challenges and opportunities of the 21st century. Establishing an International Agency for Research on Aging as an entity affiliated to one of the intergovernmental institutions, such as the World Health Organization, can be crucial for promoting international collaboration in gerontology, in particular in a search of effective and safe geroprotectors for humans.

Is Aging a Disease?¹

V. M. Novoselov*

Is Aging a Disease? A Geriatrician's Point of View¹

V. S. Myakotnykh*

Is Aging a Disease? A Biogerontologist's Point of View: Senescence \neq Disease¹

A. G. Golubev*

Is Aging a Disease? A Geneticist's Point of View¹

A. A. Moskalev^{a, b, c, d, *}

Is Aging a Disease? Biodemographers' Point of View¹

L. A. Gavrilov^{a, *} and N. S. Gavrilova^a

Attitudes towards Aging Prevention: Results of a Focus-Group Study

**A. A. Smol'kin^{a, b, *}, P. A. Zhigareva^a, E. A. Makarova^a,
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Abstract—Emerging life-extension technologies and generally used therapies aimed at preventing aging-related pathological processes have significant potential to alleviate the burden of disease in an aging world. However, promoting these technologies requires research of public opinion with the use of marketing techniques. We studied social attitudes toward life-extension technologies and use of geroprotective medicines by conducting three focus groups. The total sample included 18 people with university degrees 25–70 years of age who were living in Moscow (Russia). The tested statements were obtained in advance by surveying 30 experts in gerontology. The focus group participants were most in agreement with the statement that “aging prevention will help to maintain health and increase the active period of life.” Despite the doubts of experts, the idea that aging is a disease convinces a considerable share of the informants when the scientific evidence of the connection between aging processes and aging-related health damage is provided. Introducing new agendas into the discussion (pensions, overpopulation, etc.) turned out to be counterproductive due to new counterarguments emerging in the group discussions. The idea of radical life extension (200 years and more) was perceived skeptically. Some skepticism was attributed to mistrust and disappointment in the modern healthcare system in general. Gene therapies were perceived with caution. The word “geroprotector” is not well known even to the educated general public.

Identification of Glucosepane Cross-Link Breaking Enzymes

MATTHEW STREETER, TYLER N. GODDARD, JASON M. CRAWFORD and DAVID A. SPIEGEL

Glucosepane is a member of the class of advanced glycation end-products (AGEs), which form non-enzymatically in the human body. Glucosepane, is the most abundant AGE found in human collagen and has been implicated in the pathophysiology of various conditions ranging from diabetes to normal human aging. Glucosepane crosslinks impact the structural and mechanical properties of collagen and contribute to stiffening of collagenous tissues and vascular dysfunction. We have previously demonstrated the total synthesis of glucosepane, enabling methods for detecting and targeting glucosepane. The present study seeks to identify enzymes that are capable of catalyzing the decomposition of synthetic glucosepane crosslinks. To identify glucosepane crosslink breaking enzymes, we developed a novel screening technology based on metagenomics. Using this strategy, four enzymes were identified for in vitro validation of glucosepane degradation activity. Thus far, our efforts have focused on identifying metabolites of one class I-like enzyme in particular, since it is heterologously expressed at high levels and does not require any unusual cofactors. In vitro enzymatic assays showed that incubation of glucosepane with the class I-like enzyme led to a product consistent with citrulline. We are currently in the process of evaluating the enzyme's mechanisms of action and identifying other metabolites generated. This is the first demonstration that glucosepane can be broken down enzymatically. Our findings may provide new insight into the role of glucosepane in aging and disease and aid in the development of novel therapeutic strategies for targeting glucosepane.

[J Biol Chem](#). 2018 Jun 29. pii: jbc.RA118.002275. doi: 10.1074/jbc.RA118.002275. [Epub ahead of print]

Glycation affects fibril formation of A β peptides.

[Emendato A](#)¹, [Milordini G](#)², [Zacco E](#)², [Sicorello A](#)², [Dal Piaz F](#)³, [Guerrini R](#)⁴, [Thorogate R](#)⁵, [Picone D](#)⁶, [Pastore A](#)⁷.

⊕ Author information

Abstract

Increasing evidence shows that A β peptides, which are associated with Alzheimer disease (AD), are heavily glycosylated in patients, suggesting a role of this irreversible non-enzymatic post-translational modification in pathology. Previous reports have shown that glycation increases the toxicity of the A β peptides although little is known about the mechanism. Here, we used the natural metabolic byproduct methylglyoxal as a glycosylating agent and exploited various spectroscopic methods and atomic force microscopy to study how glycation affects the structures of the A β 40 and A β 42 peptides, the aggregation pathway, and the morphologies of the resulting aggregates. We found that glycation significantly slows down but does not prevent β -conversion to mature fibres. We propose that the previously reported higher toxicity of the glycosylated A β peptides could be explained by a longer persistence in an oligomeric form, usually believed to be the toxic species.

Aging (Albany NY), 2018 Jul 16;10(7):1640-1648. doi: 10.18632/aging.101498.

Caloric restriction effects on liver mTOR signaling are time-of-day dependent.

Tulsian R¹, Velingkaar N¹, Kondratov R¹.

⊕ Author information

Abstract

The regulation of mechanistic target of rapamycin (mTOR) signaling contributes to the metabolic effects of a calorie restriction (CR) diet. We assayed the effect of CR on the activity of mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2) in the liver of mice at six different times across the day. CR effects on mTORC1 and mTORC2 activities were time-of-day dependent. CR induced mTORC1 activity at one time, reduced at two times and has no effect during other times. CR induced mTORC2 activity at one time of the day and has no effects at other times. Circadian clocks are implemented in the regulation of mTOR signaling in mammals and mechanisms of CR. We assayed the effect of CR on mTOR signaling in the liver of mice deficient for circadian transcriptional regulators BMAL1 and CRYs. The CR induced suppression of mTORC1 activity was observed in both clock mutants, while up regulation of mTORC2 was observed in the liver of CRY deficient but not in the liver of BMAL1 deficient mice. Our finding revealed that CR has different time dependent effect on the activity of mTOR complexes 1 and 2 and suggest that circadian clock protein BMAL1 is involved in the up regulation of mTORC2 upon CR in mammals.

TORC1 inhibition enhances immune function and reduces infections in the elderly

Joan B. Mannick^{1,*†}, Melody Morris¹, Hans-Ulrich P. Hockey², Guglielmo Roma³, Martin Beibel³, Kenneth Kulmatycki¹, Moll...

+ See all authors and affiliations

Abstract

Inhibition of the mechanistic target of rapamycin (mTOR) protein kinase extends life span and ameliorates aging-related pathologies including declining immune function in model organisms. The objective of this phase 2a randomized, placebo-controlled clinical trial was to determine whether low-dose mTOR inhibitor therapy enhanced immune function and decreased infection rates in 264 elderly subjects given the study drugs for 6 weeks. A low-dose combination of a catalytic (BEZ235) plus an allosteric (RAD001) mTOR inhibitor that selectively inhibits target of rapamycin complex 1 (TORC1) downstream of mTOR was safe and was associated with a significant ($P = 0.001$) decrease in the rate of infections reported by elderly subjects for a year after study drug initiation. In addition, we observed an up-regulation of antiviral gene expression and an improvement in the response to influenza vaccination in this treatment group. Thus, selective TORC1 inhibition has the potential to improve immune function and reduce infections in the elderly.

Functional aspects of meningeal lymphatics in ageing and Alzheimer's disease

Ageing is a major risk factor for many neurological pathologies, but its mechanisms remain unclear. Unlike other tissues, the parenchyma of the central nervous system (CNS) lacks lymphatic vasculature and waste products are removed partly through a paravascular route.

(Re)discovery and characterization of meningeal lymphatic vessels has prompted an assessment of their role in waste clearance from the CNS. Here we show that meningeal lymphatic vessels drain macromolecules from the CNS (cerebrospinal and interstitial fluids) into the cervical lymph nodes in mice. Impairment of meningeal lymphatic function slows paravascular influx of macromolecules into the brain and efflux of macromolecules from the interstitial fluid, and induces cognitive impairment in mice. Treatment of aged mice with vascular endothelial growth factor C enhances meningeal lymphatic drainage of macromolecules from the cerebrospinal fluid, improving brain perfusion and learning and memory performance. Disruption of meningeal lymphatic vessels in transgenic mouse models of Alzheimer's disease promotes amyloid- β deposition in the meninges, which resembles human meningeal pathology, and aggravates parenchymal amyloid- β accumulation. Meningeal lymphatic dysfunction may be an aggravating factor in Alzheimer's disease pathology and in age-associated cognitive decline. Thus, augmentation of meningeal lymphatic function might be a promising therapeutic target for preventing or delaying age-associated neurological diseases.

Microglial activation correlates *in vivo* with both tau and amyloid in Alzheimer's disease

Alzheimer's disease is characterized by the histopathological presence of amyloid- β plaques and tau-containing neurofibrillary tangles. Microglial activation is also a recognized pathological component. The relationship between microglial activation and protein aggregation is still debated. We investigated the relationship between amyloid plaques, tau tangles and activated microglia using PET imaging. Fifty-one subjects (19 healthy controls, 16 mild cognitive impairment and 16 Alzheimer's disease subjects) participated in the study. All subjects had neuropsychometric testing, MRI, amyloid (^{18}F -flutemetamol), and microglial (^{11}C -PBR28) PET. All subjects with mild cognitive impairment and Alzheimer's disease and eight of the controls had tau (^{18}F -AV1451) PET. ^{11}C -PBR28 PET was analysed using Logan graphical analysis with an arterial plasma input function, while ^{18}F -flutemetamol and ^{18}F -AV1451 PET were analysed as target:cerebellar ratios to create parametric standardized uptake value ratio maps. Biological parametric mapping in the Statistical Parametric Mapping platform was used to examine correlations between uptake of tracers at a voxel-level. There were significant widespread clusters of positive correlation between levels of microglial activation and tau aggregation in both the mild cognitive impairment (amyloid-positive and amyloid-negative) and Alzheimer's disease subjects. The correlations were stronger in Alzheimer's disease than in mild cognitive impairment, suggesting that these pathologies increase together as disease progresses. Levels of microglial activation and amyloid deposition were also correlated, although in a different spatial distribution; correlations were stronger in mild cognitive impairment than Alzheimer's subjects, in line with a plateauing of amyloid load with disease progression. Clusters of positive correlations between microglial activation and protein aggregation often targeted similar areas of association cortex, indicating that all three processes are present in specific vulnerable brain areas. For the first time using PET imaging, we show that microglial activation can correlate with both tau aggregation and amyloid deposition. This confirms the complex relationship between these processes. These results suggest that preventative treatment for Alzheimer's disease should target all three processes.

TREM2 Ameliorates Neuronal Tau Pathology Through Suppression of Microglial Inflammatory Response

As a recently identified susceptibility gene for Alzheimer's disease (AD), triggering receptor expressed on myeloid cells 2 (*TREM2*) encodes an immune receptor that is uniquely expressed on microglia, functioning as a modulator of microglial functions including phagocytosis and inflammatory response. Several lines of evidence suggest that *TREM2* is upregulated and positively correlates with tau pathology in the brains of AD patients. Meanwhile, our recent study showed that knockdown of *TREM2* markedly exacerbated neuronal tau hyperphosphorylation in the brains of P301S-tau transgenic mice, implying that *TREM2* might exert a protective role against tau pathology under AD context. However, the precise mechanisms underlying this observation remain largely unclear. In this study, by employing a microglial-neuronal co-culture model, we showed that microglial inflammatory response induced by lipopolysaccharide led to tau hyperphosphorylation in neurons *via* activation of a major tau kinase glycogen synthase kinase 3 β , confirming the pathogenic effects of activated microglia on the progression of tau pathology. More importantly, by manipulating *TREM2* levels in microglia with a lentiviral-mediated strategy, we demonstrated that *TREM2* ameliorated the pathological effects of activated microglia on neuronal tau hyperphosphorylation *via* suppression of microglial inflammatory response. Taken together, these findings uncover the underlying mechanisms by which *TREM2* protects against tau pathology and highlight *TREM2* as a potential therapeutic target for AD.

Multiscale Analysis of Independent Alzheimer's Cohorts Finds Disruption of Molecular, Genetic, and Clinical Networks by Human Herpesvirus

Investigators have long suspected that pathogenic microbes might contribute to the onset and progression of Alzheimer's disease (AD) although definitive evidence has not been presented. Whether such findings represent a causal contribution, or reflect opportunistic passengers of neurodegeneration, is also difficult to resolve. We constructed multiscale networks of the late-onset AD-associated virome, integrating genomic, transcriptomic, proteomic, and histopathological data across four brain regions from human post-mortem tissue. We observed increased human herpesvirus 6A (HHV-6A) and human herpesvirus 7 (HHV-7) from subjects with AD compared with controls. These results were replicated in two additional, independent and geographically dispersed cohorts. We observed regulatory relationships linking viral abundance and modulators of APP metabolism, including induction of *APBB2*, *APPBP2*, *BIN1*, *BACE1*, *CLU*, *PICALM*, and *PSEN1* by HHV-6A. This study elucidates networks linking molecular, clinical, and neuropathological features with viral activity and is consistent with viral activity constituting a general feature of AD.

Alzheimer's Disease-Associated β -Amyloid Is Rapidly Seeded by *Herpesviridae* to Protect against Brain Infection

Amyloid- β peptide ($A\beta$) fibrilization and deposition as β -amyloid are hallmarks of Alzheimer's disease (AD) pathology. We recently reported $A\beta$ is an innate immune protein that protects against fungal and bacterial infections. Fibrilization pathways mediate $A\beta$ antimicrobial activities. Thus, infection can seed and dramatically accelerate β -amyloid deposition. Here, we show $A\beta$ oligomers bind herpesvirus surface glycoproteins, accelerating β -amyloid deposition and leading to protective viral entrapment activity in 5XFAD mouse and 3D human neural cell culture infection models against neurotropic herpes simplex virus 1 (HSV1) and human herpesvirus 6A and B. *Herpesviridae* are linked to AD, but it has been unclear how viruses may induce β -amyloidosis in brain. These data support the notion that $A\beta$ might play a protective role in CNS innate immunity, and suggest an AD etiological mechanism in which *herpesviridae* infection may directly promote $A\beta$ amyloidosis.

Human embryonic stem cell-derived cardiomyocytes restore function in infarcted hearts of non-human primates

Pluripotent stem cell-derived cardiomyocyte grafts can remuscularize substantial amounts of infarcted myocardium and beat in synchrony with the heart, but in some settings cause ventricular arrhythmias. It is unknown whether human cardiomyocytes can restore cardiac function in a physiologically relevant large animal model. Here we show that transplantation of ~750 million cryopreserved human embryonic stem cell-derived cardiomyocytes (hESC-CMs) enhances cardiac function in macaque monkeys with large myocardial infarctions. One month after hESC-CM transplantation, global left ventricular ejection fraction improved $10.6 \pm 0.9\%$ vs. $2.5 \pm 0.8\%$ in controls, and by 3 months there was an additional 12.4% improvement in treated vs. a 3.5% decline in controls. Grafts averaged 11.6% of infarct size, formed electromechanical junctions with the host heart, and by 3 months contained ~99% ventricular myocytes. A subset of animals experienced graft-associated ventricular arrhythmias, shown by electrical mapping to originate from a point-source acting as an ectopic pacemaker. Our data demonstrate that remuscularization of the infarcted macaque heart with human myocardium provides durable improvement in left ventricular function.

The exerkinine apelin reverses age-associated sarcopenia

Claire Vinel, Laura Lukjanenko, [...] Cedric Dray [✉](#)

Nature Medicine (2018) | [Download Citation](#) [↓](#)

Abstract

Sarcopenia, the degenerative loss of skeletal muscle mass, quality and strength, lacks early diagnostic tools and new therapeutic strategies to prevent the frailty-to-disability transition often responsible for the medical institutionalization of elderly individuals. Herein we report that production of the endogenous peptide apelin, induced by muscle contraction, is reduced in an age-dependent manner in humans and rodents and is positively associated with the beneficial effects of exercise in older persons. Mice deficient in either apelin or its receptor (APLNR) presented dramatic alterations in muscle function with increasing age. Various strategies that restored apelin signaling during aging further demonstrated that this peptide considerably enhanced muscle function by triggering mitochondriogenesis, autophagy and anti-inflammatory pathways in myofibers as well as enhancing the regenerative capacity by targeting muscle stem cells. Taken together, these findings revealed positive regulatory feedback between physical activity, apelin and muscle function and identified apelin both as a tool for diagnosis of early sarcopenia and as the target of an innovative pharmacological strategy to prevent age-associated muscle weakness and restore physical autonomy.

Towards frailty biomarkers: Candidates from genes and pathways regulated in aging and age-related diseases.

[Cardoso AL](#)¹, [Fernandes A](#)², [Aguilar-Pimentel JA](#)³, [de Angelis MH](#)⁴, [Guedes JR](#)¹, [Brito MA](#)², [Ortolano S](#)⁵, [Pani G](#)⁶, [Athanasopoulou S](#)⁷, [Gonos ES](#)⁸, [Schosserer M](#)⁹, [Grillari J](#)¹⁰, [Peterson P](#)¹¹, [Tuna BG](#)¹², [Dogan S](#)¹³, [Meyer A](#)¹⁴, [van Os R](#)¹⁵, [Trendelenburg AU](#)¹⁶.

⊕ Author information

Abstract

OBJECTIVE: Use of the frailty index to measure an accumulation of deficits has been proven a valuable method for identifying elderly people at risk for increased vulnerability, disease, injury, and mortality. However, complementary molecular frailty biomarkers or ideally biomarker panels have not yet been identified. We conducted a systematic search to identify biomarker candidates for a frailty biomarker panel.

METHODS: Gene expression databases were searched (<http://genomics.senescence.info/genes> including GenAge, AnAge, LongevityMap, CellAge, DrugAge, Digital Aging Atlas) to identify genes regulated in aging, longevity, and age-related diseases with a focus on secreted factors or molecules detectable in body fluids as potential frailty biomarkers. Factors broadly expressed, related to several "hallmark of aging" pathways as well as used or predicted as biomarkers in other disease settings, particularly age-related pathologies, were identified. This set of biomarkers was further expanded according to the expertise and experience of the authors. In the next step, biomarkers were assigned to six "hallmark of aging" pathways, namely (1) inflammation, (2) mitochondria and apoptosis, (3) calcium homeostasis, (4) fibrosis, (5) NMJ (neuromuscular junction) and neurons, (6) cytoskeleton and hormones, or (7) other principles and an extensive literature search was performed for each candidate to explore their potential and priority as frailty biomarkers.

RESULTS: A total of 44 markers were evaluated in the seven categories listed above, and 19 were awarded a high priority score, 22 identified as medium priority and three were low priority. In each category high and medium priority markers were identified.

CONCLUSION: Biomarker panels for frailty would be of high value and better than single markers. Based on our search we would propose a core panel of frailty biomarkers consisting of (1) CXCL10 (C-X-C motif chemokine ligand 10), IL-6 (interleukin 6), CX3CL1 (C-X3-C motif chemokine ligand 1), (2) GDF15 (growth differentiation factor 15), FNDC5 (fibronectin type III domain containing 5), vimentin (VIM), (3) regucalcin (RGN/SMP30), calreticulin, (4) PLAU (plasminogen activator, urokinase), AGT (angiotensinogen), (5) BDNF (brain derived neurotrophic factor), progranulin (PGRN), (6) α -klotho (KL), FGF23 (fibroblast growth factor 23), FGF21, leptin (LEP), (7) miRNA (micro Ribonucleic acid) panel (to be further defined), AHCY (adenosylhomocysteinase) and KRT18 (keratin 18). An expanded panel would also include (1) pentraxin (PTX3), sVCAM/ICAM (soluble vascular cell adhesion molecule 1/Intercellular adhesion molecule 1), defensin α , (2) APP (amyloid beta precursor protein), LDH (lactate dehydrogenase), (3) S100B (S100 calcium binding protein B), (4) TGF β (transforming growth factor beta), PAI-1 (plasminogen activator inhibitor 1), TGM2 (transglutaminase 2), (5) sRAGE (soluble receptor for advanced glycosylation end products), HMGB1 (high mobility group box 1), C3/C1Q (complement factor 3/1Q), ST2 (Interleukin 1 receptor like 1), agrin (AGRN), (6) IGF-1 (insulin-like growth factor 1), resistin (RETN), adiponectin (ADIPOQ), ghrelin (GHRL), growth hormone (GH), (7) microparticle panel (to be further defined), GpnmB (glycoprotein nonmetastatic melanoma protein B) and lactoferrin (LTF). We believe that these predicted panels need to be experimentally explored in animal models and frail cohorts in order to ascertain their diagnostic, prognostic and therapeutic potential.

J Gerontol A Biol Sci Med Sci. 2018 Jul 27. doi: 10.1093/gerona/gly174. [Epub ahead of print]

APOE Alleles and Extreme Human Longevity.

Sebastiani P¹, Gurinovich A^{1,2}, Nygaard M³, Sasaki T⁴, Sweigart B¹, Bae H⁵, Andersen SL⁶, Villa F⁷, Atzmon G^{8,9}, Christensen K³, Arai Y⁴, Barzilai N⁹, Puca A^{7,10}, Christiansen L³, Hirose N⁴, Perls TT⁶.

⊕ Author information

Abstract

We assembled a collection of 28,297 participants from 7 studies of longevity and healthy aging comprising New England Centenarian, Long Life Family, Longevity Gene Population, Southern Italian Centenarian, Japanese Centenarian, the Danish Longevity and the Health and Retirement Studies to investigate the association between the APOE alleles $\epsilon 2$, $\epsilon 3$ and $\epsilon 4$ and extreme human longevity and age at death. By using 3 different genetic models and two definitions of extreme longevity based on either a threshold model or age at death, we show that $\epsilon 4$ is associated with a substantially decreased odds for extreme longevity, and increased risk for death that persists even beyond ages reached by less than 1% of the population. We also show that carrying the $\epsilon 2\epsilon 3$ or $\epsilon 2\epsilon 3$ genotype is associated with significantly increased odds to reach extreme longevity, with decreased risk for death compared to carrying the genotype $\epsilon 2\epsilon 3$ but with only a modest reduction in risk for death beyond an age reached by less than 1% of the population.

[Aging Cell](#). 2018 Jun 30:e12819. doi: 10.1111/accel.12819. [Epub ahead of print]

Gene Expression-Based Drug Repurposing to Target Ageing.

[Dönertaş HM](#)¹, [Fuentelba Valenzuela M](#)^{1,2}, [Partridge L](#)^{2,3}, [Thornton JM](#)¹.

⊕ Author information

Abstract

Ageing is the largest risk factor for a variety of non-communicable diseases. Model organism studies have shown that genetic and chemical perturbations can extend both life- and health-span. Ageing is a complex process, with parallel and interacting mechanisms contributing to its aetiology, posing a challenge for the discovery of new pharmacological candidates to ameliorate its effects. In this study, instead of a target-centric approach, we adopt a systems level drug repurposing methodology to discover drugs that could combat ageing in human brain. Using multiple gene expression datasets from brain tissue, taken from patients of different ages, we first identified the expression changes that characterise ageing. Then, we compared these changes in gene expression with drug perturbed expression profiles in the Connectivity Map. We thus identified 24 drugs with significantly associated changes. Some of these drugs may function as anti-ageing drugs by reversing the detrimental changes that occur during ageing, others by mimicking the cellular defense mechanisms. The drugs that we identified included significant number of already identified pro-longevity drugs, indicating that the method can discover de novo drugs that meliorate ageing. The approach has the advantages that, by using data from human brain ageing data it focuses on processes relevant in human ageing and that it is unbiased, making it possible to discover new targets for ageing studies. This article is protected by copyright. All rights reserved.


A versatile drug delivery system targeting senescent cells

Senescent cells accumulate in multiple aging-associated diseases, and eliminating these cells has recently emerged as a promising therapeutic approach. Here, we take advantage of the high lysosomal β -galactosidase activity of senescent cells to design a drug delivery system based on the encapsulation of drugs with galacto-oligosaccharides. We show that gal-encapsulated fluorophores are preferentially released within senescent cells in mice. In a model of chemotherapy-induced senescence, gal-encapsulated cytotoxic drugs target senescent tumor cells and improve tumor xenograft regression in combination with palbociclib. Moreover, in a model of pulmonary fibrosis in mice, gal-encapsulated cytotoxics target senescent cells, reducing collagen deposition and restoring pulmonary function. Finally, gal-encapsulation reduces the toxic side effects of the cytotoxic drugs. Drug delivery into senescent cells opens new diagnostic and therapeutic applications for senescence-associated disorders.

Senolytics improve physical function and increase lifespan in old age

Physical function declines in old age, portending disability, increased health expenditures, and mortality. Cellular senescence, leading to tissue dysfunction, may contribute to these consequences of aging, but whether senescence can directly drive age-related pathology and be therapeutically targeted is still unclear. Here we demonstrate that transplanting relatively small numbers of senescent cells into young mice is sufficient to cause persistent physical dysfunction, as well as to spread cellular senescence to host tissues. Transplanting even fewer senescent cells had the same effect in older recipients and was accompanied by reduced survival, indicating the potency of senescent cells in shortening health- and lifespan. The senolytic cocktail, dasatinib plus quercetin, which causes selective elimination of senescent cells, decreased the number of naturally occurring senescent cells and their secretion of frailty-related proinflammatory cytokines in explants of human adipose tissue. Moreover, intermittent oral administration of senolytics to both senescent cell-transplanted young mice and naturally aged mice alleviated physical dysfunction and increased post-treatment survival by 36% while reducing mortality hazard to 65%. Our study provides proof-of-concept evidence that senescent cells can cause physical dysfunction and decreased survival even in young mice, while senolytics can enhance remaining health- and lifespan in old mice.

FoxM1 repression during human aging leads to mitotic decline and aneuploidy-driven full senescence

Joana Catarina Macedo, Sara Vaz, Bjorn Bakker, Rui Ribeiro, Petra Lammigje Bakker, Jose Miguel Escandell, Miguel Godinho Ferreira, René Medema, Floris Fojjer & Elsa Logarinho 

Aneuploidy, an abnormal chromosome number, has been linked to aging and age-associated diseases, but the underlying molecular mechanisms remain unknown. Here we show, through direct live-cell imaging of young, middle-aged, and old-aged primary human dermal fibroblasts, that aneuploidy increases with aging due to general dysfunction of the mitotic machinery. Increased chromosome mis-segregation in elderly mitotic cells correlates with an early senescence-associated secretory phenotype (SASP) and repression of Forkhead box M1 (FoxM1), the transcription factor that drives G2/M gene expression. FoxM1 induction in elderly and Hutchison–Gilford progeria syndrome fibroblasts prevents aneuploidy and, importantly, ameliorates cellular aging phenotypes. Moreover, we show that senescent fibroblasts isolated from elderly donors' cultures are often aneuploid, and that aneuploidy is a key trigger into full senescence phenotypes. Based on this feedback loop between cellular aging and aneuploidy, we propose modulation of mitotic efficiency through FoxM1 as a potential strategy against aging and progeria syndromes.

Phenotypic Age: a novel signature of mortality and morbidity risk

Zuyun Liu, Pei-Lun Kuo, Steve Horvath, Eileen Crimmins, Luigi Ferrucci, Morgan Levine

Background: A person's rate of aging has important implications for his/her risk of death and disease, thus, quantifying aging using observable characteristics has important applications for clinical, basic, and observational research. We aimed to validate a novel aging measure, 'Phenotypic Age', constructed based on routine clinical chemistry measures, by assessing its applicability for differentiating risk for morbidity and mortality in both healthy and unhealthy populations of various ages.

Methods: A nationally representative US sample, NHANES III, was used to derive 'Phenotypic Age' based on a linear combination of chronological age and nine multi-system clinical chemistry measures, selected via cox proportional elastic net. Mortality predictions were validated using an independent sample (NHANES IV), consisting of 11,432 participants, for whom we observed a total of 871 deaths, ascertained over 12.6 year of follow-up. Proportional hazard models and ROC curves were used to evaluate predictions.

Results: Phenotypic Age was significantly associated with all-cause mortality and cause-specific mortality. These results were robust to age and sex stratification, and remained even when excluding short-term mortality. Similarly, Phenotypic Age was associated with mortality among seemingly 'healthy' participants, defined as those who were disease-free and had normal BMI at baseline, as well as the oldest-old (aged 85+), a group with high disease burden.

Conclusions: Phenotypic Age is a reliable predictor of all-cause and cause-specific mortality in multiple subgroups of the population. Risk stratification by this composite measure is far superior to that of the individual measures that go into it, as well as traditional measures of health. It is able to differentiate individuals who appear healthy, who may have otherwise been missed using traditional health assessments. Further, it can differentiate risk among persons with shared disease burden. Overall, this easily measured metric may be useful in the clinical setting and facilitate secondary and tertiary prevention strategies.

Unconventional secretion of misfolded proteins promotes adaptation to proteasome dysfunction in mammalian cells


To safeguard proteomic integrity, cells rely on the proteasome to degrade aberrant polypeptides, but it is unclear how cells remove defective proteins that have escaped degradation owing to proteasome insufficiency or dysfunction. Here we report a pathway termed misfolding-associated protein secretion, which uses the endoplasmic reticulum (ER)-associated deubiquitylase USP19 to preferentially export aberrant cytosolic proteins. Intriguingly, the catalytic domain of USP19 possesses an unprecedented chaperone activity, allowing recruitment of misfolded proteins to the ER surface for deubiquitylation. Deubiquitylated cargos are encapsulated into ER-associated late endosomes and secreted to the cell exterior. USP19-deficient cells cannot efficiently secrete unwanted proteins, and grow more slowly than wild-type cells following exposure to a proteasome inhibitor. Together, our findings delineate a protein quality control (PQC) pathway that, unlike degradation-based PQC mechanisms, promotes protein homeostasis by exporting misfolded proteins through an unconventional protein secretion process.

Reversing wrinkled skin and hair loss in mice by restoring mitochondrial function

Mitochondrial DNA (mtDNA) depletion is involved in mtDNA depletion syndromes, mitochondrial diseases, aging and aging-associated chronic diseases, and other human pathologies. To evaluate the consequences of depletion of mtDNA in the whole animal, we created an inducible mtDNA-deleter mouse expressing, in the polymerase domain of POLG1, a dominant-negative mutation to induce depletion of mtDNA in various tissues. These mice showed reduced mtDNA content, reduced mitochondrial gene expression, and instability of supercomplexes involved in oxidative phosphorylation (OXPHOS) resulting in reduced OXPHOS enzymatic activities. We demonstrate that ubiquitous depletion of mtDNA in mice leads to predominant and profound effects on the skin resulting in wrinkles and visual hair loss with an increased number of dysfunctional hair follicles and inflammatory responses. Development of skin wrinkle was associated with the significant epidermal hyperplasia, hyperkeratosis, increased expression of matrix metalloproteinases, and decreased expression of matrix metalloproteinase inhibitor TIMP1. We also discovered markedly increased skin inflammation that appears to be a contributing factor in skin pathology. Histopathologic analyses revealed dysfunctional hair follicles. mtDNA-deleter mice also show changes in expression of aging-associated markers including IGF1R, KLOTHO, VEGF, and MRPS5. mtDNA-repleter mice showed that, by turning off the mutant POLG1 transgene expression, mitochondrial function, as well as the skin and hair pathology, is reversed to wild-type level. To our knowledge that restoration of mitochondrial functions can reverse the skin and hair pathology is unprecedented.

Physical Activity as a Determinant of Successful Aging over Ten Years

Bamini Gopinath , Annette Kifley, Victoria M. Flood & Paul Mitchell

Scientific Reports **8**, Article number: 10522 (2018) | [Download Citation](#) 

Abstract

We aimed to examine the temporal association between physical activity and successful aging. The analyses involved 1,584 adults aged 49 + years living west of Sydney (Australia), who did not have cancer, coronary artery disease and stroke at baseline and who were followed over 10 years. Participants provided information on the performance of moderate or vigorous activities and walking exercise and this was used to determine total metabolic equivalents (METs) minutes of activity per week. Successful aging status was determined through interviewer-administered questionnaire and was classified as the absence of: depressive symptoms, disability, cognitive impairment, respiratory symptoms and systemic conditions (e.g. cancer, coronary artery disease). 249 (15.7%) participants (mean age 59.9 ± 6.1) had aged successfully 10 years later. After multivariable adjustment; older adults in the highest level of total physical activity (≥ 5000 MET minutes/week; $n = 71$) compared to those in the lowest level of total physical activity (< 1000 MET minutes/week; $n = 934$) had 2-fold greater odds of aging successfully than normal aging, odds ratio, OR, 2.08 (95% confidence intervals, CI, 1.12–3.88). Older adults who engaged in high levels of total physical activity, well above the current recommended minimum level had a greater likelihood of aging successfully 10 years later.

Association of fish and long-chain omega-3 fatty acids intakes with total and cause-specific mortality: prospective analysis of 421 309 individuals

Objectives

To examine the associations of fish and LCn-3 PUFAs intakes with total and cause-specific mortality.

Methods

A total of 240 729 men and 180 580 women from NIH-AARP Diet and Health Study were prospectively followed-up for 16 years. Dietary intakes were assessed using a validated NIH Diet History Questionnaire.

Results

A total of 54 230 men and 30 882 women died during 6.07 million person-years of follow-up. Higher fish and LCn-3 PUFAs intakes were significantly associated with lower total mortality ($P < 0.0001$). Comparing the highest with lowest quintiles of fish intake, men had 9% (95% confidence interval, 6–11%) lower total mortality, 10% (6–15%) lower cardiovascular disease (CVD) mortality, 6% (1–10%) lower cancer mortality, 20% (11–28%) lower respiratory disease mortality and 37% (17–53%) lower chronic liver disease mortality, while women had 8% (5–12%) lower total mortality, 10% (3–17%) lower CVD mortality and 38% (20–52%) lower Alzheimer's disease mortality. Fried fish consumption was not related to mortality in men whereas positively associated with mortality from all causes ($P = 0.011$), CVD and respiratory disease in women. LCn-3 PUFAs intake was associated with 15% and 18% lower CVD mortality in men and women across extreme quintiles, respectively.

Conclusion

Consumption of fish and LCn-3 PUFAs was robustly associated with lower mortality from major causes. Our findings support current guidelines for fish consumption while advice on non-frying preparation methods is needed.

REVIEWS/COMMENTS/
METHODS/EDITORIALS

Hallmarks of Brain Aging: Adaptive and Pathological Modification by Metabolic States.

Review article

Mattson MP, et al. Cell Metab. 2018.

[Show full citation](#)

Abstract

During aging, the cellular milieu of the brain exhibits tell-tale signs of compromised bioenergetics, impaired adaptive neuroplasticity and resilience, aberrant neuronal network activity, dysregulation of neuronal Ca²⁺ homeostasis, the accrual of oxidatively modified molecules and organelles, and inflammation. These alterations render the aging brain vulnerable to Alzheimer's and Parkinson's diseases and stroke. Emerging findings are revealing mechanisms by which sedentary overindulgent lifestyles accelerate brain aging, whereas lifestyles that include intermittent bioenergetic challenges (exercise, fasting, and intellectual challenges) foster healthy brain aging. Here we provide an overview of the cellular and molecular biology of brain aging, how those processes interface with disease-specific neurodegenerative pathways, and how metabolic states influence brain health.

Gerontology, 2018 Jul 11:1-14. doi: 10.1159/000490349. [Epub ahead of print]

The Glymphatic System and Waste Clearance with Brain Aging: A Review.

Benveniste H¹, Liu X^{1,2}, Koundal S¹, Sanggaard S¹, Lee H¹, Wardlaw J³.

⊕ Author information



Abstract

The glymphatic system is a glial-dependent waste clearance pathway in the brain, in place of lymphatic vessels, dedicated to drain away soluble waste proteins and metabolic products. Specifically, the glymphatic network serves as a "front end" for waste clearance, and is connected downstream to an authentic lymphatic network, associated with dura covering the brain as well as cranial nerves and large vessels at the skull exits. The anatomical and functional interconnections between these two networks are not completely understood. Several key physiological processes have been identified that control glymphatic transport function and waste clearance from brain. In this review, we aim to provide an overview and discussion of the concept behind the glymphatic system, current evidence, and controversies, while specifically focusing on the consequences of aging and evidence of its existence in human brain. Discovering novel strategies for optimizing and maintaining efficient brain waste clearance across the lifespan may in the future prove to be important for preventing cognitive decline and sustaining healthy aging.

Mechanisms of protein toxicity in neurodegenerative diseases

Authors

[Authors and affiliations](#)

Chang Geon Chung, Hyosang Lee , Sung Bae Lee 

[Open Access](#) | [Review](#)

First Online: 12 June 2018



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Abstract

Protein toxicity can be defined as all the pathological changes that ensue from accumulation, mis-localization, and/or multimerization of disease-specific proteins. Most neurodegenerative diseases manifest protein toxicity as one of their key pathogenic mechanisms, the details of which remain unclear. By systematically deconstructing the nature of toxic proteins, we aim to elucidate and illuminate some of the key mechanisms of protein toxicity from which therapeutic insights may be drawn. In this review, we focus specifically on protein toxicity from the point of view of various cellular compartments such as the nucleus and the mitochondria. We also discuss the cell-to-cell propagation of toxic disease proteins that complicates the mechanistic understanding of the disease progression as well as the spatiotemporal point at which to therapeutically intervene. Finally, we discuss selective neuronal vulnerability, which still remains largely enigmatic.

Autophagy as a promoter of longevity: insights from model organisms

Malene Hansen ✉, David C. Rubinsztein ✉ & David W. Walker ✉

Autophagy is a conserved process that catabolizes intracellular components to maintain energy homeostasis and to protect cells against stress. Autophagy has crucial roles during development and disease, and evidence accumulated over the past decade indicates that autophagy also has a direct role in modulating ageing. In particular, elegant studies using yeasts, worms, flies and mice have demonstrated a broad requirement for autophagy-related genes in the lifespan extension observed in a number of conserved longevity paradigms. Moreover, several new and interesting concepts relevant to autophagy and its role in modulating longevity have emerged. First, select tissues may require or benefit from autophagy activation in longevity paradigms, as tissue-specific overexpression of single autophagy genes is sufficient to extend lifespan. Second, selective types of autophagy may be crucial for longevity by specifically targeting dysfunctional cellular components and preventing their accumulation. And third, autophagy can influence organismal health and ageing even non-cell autonomously, and thus, autophagy stimulation in select tissues can have beneficial, systemic effects on lifespan. Understanding these mechanisms will be important for the development of approaches to improve human healthspan that are based on the modulation of autophagy.

The transition to modernity and chronic disease: mismatch and natural selection

Stephen Corbett, Alexandre Courtiol, Virpi Lummaa, Jacob Moorad & Stephen Stearns [✉](#)

Nature Reviews Genetics **19**, 419–430 (2018) | [Download Citation](#) [↓](#)

Abstract

The Industrial Revolution and the accompanying nutritional, epidemiological and demographic transitions have profoundly changed human ecology and biology, leading to major shifts in life history traits, which include age and size at maturity, age-specific fertility and lifespan. Mismatch between past adaptations and the current environment means that gene variants linked to higher fitness in the past may now, through antagonistic pleiotropic effects, predispose post-transition populations to non-communicable diseases, such as Alzheimer disease, cancer and coronary artery disease. Increasing evidence suggests that the transition to modernity has also altered the direction and intensity of natural selection acting on many traits, with important implications for public and global health.

Inflammaging: a new immune–metabolic viewpoint for age-related diseases

Claudio Franceschi, Paolo Garagnani, Paolo Parini, Cristina Giuliani  & Aurelia Santoro

Ageing and age-related diseases share some basic mechanistic pillars that largely converge on inflammation. During ageing, chronic, sterile, low-grade inflammation – called inflammaging – develops, which contributes to the pathogenesis of age-related diseases. From an evolutionary perspective, a variety of stimuli sustain inflammaging, including pathogens (non-self), endogenous cell debris and misplaced molecules (self) and nutrients and gut microbiota (quasi-self). A limited number of receptors, whose degeneracy allows them to recognize many signals and to activate the innate immune responses, sense these stimuli. In this situation, metaflammation (the metabolic inflammation accompanying metabolic diseases) is thought to be the form of chronic inflammation that is driven by nutrient excess or overnutrition; metaflammation is characterized by the same mechanisms underpinning inflammaging. The gut microbiota has a central role in both metaflammation and inflammaging owing to its ability to release inflammatory products, contribute to circadian rhythms and crosstalk with other organs and systems. We argue that chronic diseases are not only the result of ageing and inflammaging; these diseases also accelerate the ageing process and can be considered a manifestation of accelerated ageing. Finally, we propose the use of new biomarkers (DNA methylation, glycomics, metabolomics and lipidomics) that are capable of assessing biological versus chronological age in metabolic diseases.

The role of non-resolving inflammation in atherosclerosis

Canan Kasikara,¹ Amanda C. Doran,¹ Bishuang Cai,¹ and Ira Tabas^{1,2,3}

First published July 2, 2018 - [More info](#)

Non-resolving inflammation drives the development of clinically dangerous atherosclerotic lesions by promoting sustained plaque inflammation, large necrotic cores, thin fibrous caps, and thrombosis. Resolution of inflammation is not merely a passive return to homeostasis, but rather an active process mediated by specific molecules, including fatty acid–derived specialized pro-resolving mediators (SPMs). In advanced atherosclerosis, there is an imbalance between levels of SPMs and proinflammatory lipid mediators, which results in sustained leukocyte influx into lesions, inflammatory macrophage polarization, and impaired efferocytosis. In animal models of advanced atherosclerosis, restoration of SPMs limits plaque progression by suppressing inflammation, enhancing efferocytosis, and promoting an increase in collagen cap thickness. This Review discusses the roles of non-resolving inflammation in atherosclerosis and highlights the unique therapeutic potential of SPMs in blocking the progression of clinically dangerous plaques.

Atherosclerosis and inflammation: overview and updates

Glaucylara Reis Geovanini, Peter Libby

Clinical Science

Jun 21, 2018,

132

(12)

1243-1252;

DOI: 10.1042/CS20180306

Article

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Abstract

The concept that inflammation participates pivotally in the pathogenesis of atherosclerosis and its complications has gained considerable attention, but has not yet entered clinical practice. Experimental work has elucidated molecular and cellular pathways of inflammation that promote atherosclerosis. The recognition of atherogenesis as an active process rather than a cholesterol storage disease or a repository of calcium has highlighted some key inflammatory mechanisms. For example, mononuclear phagocytes contribute to all stages of this disease, illustrating the link between inflammation and atherosclerosis. From a clinical perspective, harnessing inflammation may now help target therapeutics, change guidelines, and enter daily practice. Multiple lines of incontrovertible evidence have proven a causal role for low-density lipoprotein (LDL) cholesterol in atherosclerosis, and we have highly effective tools for lowering LDL, consequently reducing events. Yet, even with intense LDL reduction, events still occur. Inflammation can explain some of this residual risk. An anti-inflammatory intervention has now proven capable of improving outcomes in individuals well treated with LDL-lowering agents. A suite of trials are now pursuing anti-inflammatory therapies in this context. Assessment and treatment of residual inflammatory risk are poised to provide new inroads into preventive cardiology. This brief review aims to explore the potential mechanisms underlying the association of inflammation and atherogenesis, and their clinical consequences.

Somatic Editing of *Ldlr* With Adeno-Associated Viral-CRISPR Is an Efficient Tool for Atherosclerosis Research

Kelsey E. Jarrett, Ciaran Lee, Marco De Giorgi, Ayrea Hurley, Baiba K. Gillard, Alexandria M. Doerfler, Ang Li, Henry J. Pownall, Gang Bao and William R. Lagor ✉

Originally published 19 Jul 2018 | Arteriosclerosis, Thrombosis, and Vascular Biology. 2018;0:ATVBAHA.118.311221

Abstract

Objective—

Atherosclerosis studies in *Ldlr* knockout mice require breeding to homozygosity and congenic status on C57BL6/J background, a process that is both time and resource intensive. We aimed to develop a new method for generating atherosclerosis through somatic deletion of *Ldlr* in livers of adult mice.

Approach and Results—

Overexpression of PCSK9 (proprotein convertase subtilisin/kexin type 9) is currently used to study atherosclerosis, which promotes degradation of LDLR (low-density lipoprotein receptor) in the liver. We sought to determine whether CRISPR/Cas9 (clustered regularly interspaced short palindromic repeats-associated 9) could also be used to generate atherosclerosis through genetic disruption of *Ldlr* in adult mice. We engineered adeno-associated viral (AAV) vectors expressing *Staphylococcus aureus* Cas9 and a guide RNA targeting the *Ldlr* gene (AAV-CRISPR). Both male and female mice received either (1) saline, (2) AAV-CRISPR, or (3) AAV-hPCSK9 (human PCSK9)-D374Y. A fourth group of germline *Ldlr*-KO mice was included for comparison. Mice were placed on a Western diet and followed for 20 weeks to assess plasma lipids, PCSK9 protein levels, atherosclerosis, and editing efficiency. Disruption of *Ldlr* with AAV-CRISPR was robust, resulting in severe hypercholesterolemia and atherosclerotic lesions in the aorta. AAV-hPCSK9 also produced hypercholesterolemia and atherosclerosis as expected. Notable sexual dimorphism was observed, wherein AAV-CRISPR was superior for *Ldlr* removal in male mice, while AAV-hPCSK9 was more effective in female mice.

Conclusions—

This all-in-one AAV-CRISPR vector targeting *Ldlr* is an effective and versatile tool to model atherosclerosis with a single injection and provides a useful alternative to the use of germline *Ldlr*-KO mice.

[Curr Protoc Mouse Biol.](#) 2018 Jun;8(2):e45. doi: 10.1002/cpmo.45.

Assessing Healthspan and Lifespan Measures in Aging Mice: Optimization of Testing Protocols, Replicability, and Rater Reliability.

[Sukoff Rizzo SJ](#)¹, [Anderson LC](#)¹, [Green TL](#)¹, [McGarr T](#)¹, [Wells G](#)¹, [Winter SS](#)¹.



⊕ Author information

Abstract


The relationship between chronological age (lifespan) and biological age (healthspan) varies amongst individuals. Understanding the normal trajectory and characteristic traits of aging mice throughout their lifespan is important for selecting the most reliable and reproducible measures to test hypotheses. The protocols herein describe assays used for aging studies at The Jackson Laboratory's Mouse Neurobehavioral Phenotyping Facility and include assessments of frailty, cognition, and sensory (hearing, vision, olfaction), motor, and fine motor function that can be used for assessing phenotypes in aged mice across their lifespan as well as provide guidance for setting up and validating these behavioral measures. Researchers aiming to study aging phenotypes require access to aged mice as a reference when initiating these types of studies in order to observe normal aging characteristics that cannot be observed in young adult mouse populations.

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Hsp90 inhibitors as senolytic drugs to extend healthy aging

Heike Fuhrmann-Stroissnigg , Laura J. Niedernhofer & Paul D. Robbins 

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 Download citation  <https://doi.org/10.1080/15384101.2018.1475828>



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ABSTRACT

Aging is characterized by progressive decay of biological systems and although it is not considered a disease, it is one of the main risk factors for chronic diseases and many types of cancers. The accumulation of senescent cells in various tissues is thought to be a major factor contributing to aging and age-related diseases. Removal of senescent cells during aging by either genetic or therapeutic methods have led to an improvement of several age related disease in mice. In this preview, we highlight the significance of developing senotherapeutic approaches to specifically kill senescent cells (senolytics) or suppress the senescence-associated secretory phenotype (SASP) that drives sterile inflammation (senomorphics) associated with aging to extend healthspan and potentially lifespan. Also, we provide an overview of the senotherapeutic drugs identified to date. In particular, we discuss and expand upon the recent identification of inhibitors of the HSP90 co-chaperone as a new class of senolytics.

[J Clin Invest](#). 2018 Jul 30. pii: 120842. doi: 10.1172/JCI120842. [Epub ahead of print]

The role of mitochondria in aging.

[Jang JY](#)¹, [Blum A](#)², [Liu J](#)¹, [Finkel T](#)¹.

⊕ Author information

Abstract

The biological basis of human aging remains one of the greatest unanswered scientific questions. Increasing evidence, however, points to a role for alterations in mitochondrial function as a potential central regulator of the aging process. Here, we focus primarily on three aspects of mitochondrial biology that link this ancient organelle to how and why we age. In particular, we discuss the role of mitochondria in regulating the innate immune system, the mechanisms linking mitochondrial quality control to age-dependent pathology, and the possibility that mitochondrial-to-nuclear signaling might regulate the rate of aging.

Background

Nicotinamide adenine dinucleotide (NAD⁺) is an essential pyridine nucleotide that is currently investigated as an important target to extend lifespan and health span. Age-related NAD⁺ depletion due to the accumulation of oxidative stress is associated with reduced energy production, impaired DNA repair and genomic instability.

Scope of review

NAD⁺ levels can be elevated therapeutically using NAD⁺ precursors or through lifestyle modifications including exercise and caloric restriction. However, high amounts of NAD⁺ may be detrimental in cancer progression and may have deleterious immunogenic roles.



Major conclusions

Standardized quantitation of NAD⁺ and related metabolites may therefore represent an important component of NAD⁺ therapy.

General significance

Quantitation of NAD⁺ may serve dual roles not only as an ageing biomarker, but also as a diagnostic tool for the prevention of malignant disorders.


Sex gap in aging and longevity: can sex chromosomes play a role?

Gabriel A.B. Marais  , Jean-Michel Gaillard, Cristina Vieira, Ingrid Plotton, Damien Sanlaville, François Gueyffier and Jean-Francois Lemaitre

It is well known that women live longer than men. This gap is observed in most human populations and can even reach 10–15 years. In addition, most of the known super centenarians (i.e., humans who lived for > 110 years) are women. The differences in life expectancy between men and women are often attributed to cultural differences in common thinking. However, sex hormones seem to influence differences in the prevalence of diseases, in the magnitude of aging, and in the longevity between men and women. Moreover, far from being human specific, the sex gap in longevity is extremely common in non-human animals, especially in mammals. Biological factors clearly contribute to such a sex gap in aging and longevity. Different hypotheses have been proposed to explain why males and females age and die differently. The cost of sexual selection and sexual dimorphism has long been considered the best explanation for the observed sex gap in aging/longevity. However, the way mitochondria are transmitted (i.e., through females in most species) could have an effect, called the mother's curse. Recent data suggest that sex chromosomes may also contribute to the sex gap in aging/longevity through several potential mechanisms, including the unguarded X/Z, the toxic Y/W and the loss of Y/W. We discuss future research directions to test these ideas.

Cellular and epigenetic drivers of stem cell ageing

Maria Ermolaeva , Francesco Neri , Alessandro Ori  & K. Lenhard Rudolph 

Nature Reviews Molecular Cell Biology (2018) | [Download Citation](#) 

Abstract

Adult tissue stem cells have a pivotal role in tissue maintenance and regeneration throughout the lifespan of multicellular organisms. Loss of tissue homeostasis during post-reproductive lifespan is caused, at least in part, by a decline in stem cell function and is associated with an increased incidence of diseases. Hallmarks of ageing include the accumulation of molecular damage, failure of quality control systems, metabolic changes and alterations in epigenome stability. In this Review, we discuss recent evidence in support of a novel concept whereby cell-intrinsic damage that accumulates during ageing and cell-extrinsic changes in ageing stem cell niches and the blood result in modifications of the stem cell epigenome. These cumulative epigenetic alterations in stem cells might be the cause of the deregulation of developmental pathways seen during ageing. In turn, they could confer a selective advantage to mutant and epigenetically drifted stem cells with altered self-renewal and functions, which contribute to the development of ageing-associated organ dysfunction and disease.

OTHER RESEARCH

Opinion

Reversible, Spatial and Temporal Control over Protein Activity Using Light

Mark W.H. Hoorens^{1,2} and Wiktor Szymanski^{1,2,*}

In biomedical sciences, the function of a protein of interest is investigated by altering its net activity and assessing the consequences for the cell or organism. To change the activity of a protein, a wide variety of chemical and genetic tools have been developed. The drawback of most of these tools is that they do not allow for reversible, spatial and temporal control. Here, we describe selected developments in photopharmacology that aim at establishing such control over protein activity through bioactive molecules with photo-controlled potency. We also discuss why such control is desired and what challenges still need to be overcome for photopharmacology to reach its maturity as a chemical biology research tool.

Synthetic far-red light-mediated CRISPR-dCas9 device for inducing functional neuronal differentiation



Jiawei Shao, Meiyang Wang, Guiling Yu, Sucheng Zhu, Yuanhuan Yu, Boon Chin Heng, Jiali Wu, and Haifeng Ye

The ability to control the activity of CRISPR-dCas9 with precise spatiotemporal resolution will enable tight genome regulation of user-defined endogenous genes for studying the dynamics of transcriptional regulation. Optogenetic devices with minimal phototoxicity and the capacity for deep tissue penetration are extremely useful for precise spatiotemporal control of cellular behavior and for future clinic translational research. Therefore, capitalizing on synthetic biology and optogenetic design principles, we engineered a far-red light (FRL)-activated CRISPR-dCas9 effector (FACE) device that induces transcription of exogenous or endogenous genes in the presence of FRL stimulation. This versatile system provides a robust and convenient method for precise spatiotemporal control of endogenous gene expression and also has been demonstrated to mediate targeted epigenetic modulation, which can be utilized to efficiently promote differentiation of induced pluripotent stem cells into functional neurons by up-regulating a single neural transcription factor, *NEUROG2*. This FACE system might facilitate genetic/epigenetic reprogramming in basic biological research and regenerative medicine for future biomedical applications.

Human pluripotent reprogramming with CRISPR activators

CRISPR-Cas9-based gene activation (CRISPRa) is an attractive tool for cellular reprogramming applications due to its high multiplexing capacity and direct targeting of endogenous loci. Here we present the reprogramming of primary human skin fibroblasts into induced pluripotent stem cells (iPSCs) using CRISPRa, targeting endogenous OCT4, SOX2, KLF4, MYC, and LIN28A promoters. The low basal reprogramming efficiency can be improved by an order of magnitude by additionally targeting a conserved Alu-motif enriched near genes involved in embryo genome activation (EEA-motif). This effect is mediated in part by more efficient activation of NANOG and REX1. These data demonstrate that human somatic cells can be reprogrammed into iPSCs using only CRISPRa. Furthermore, the results unravel the involvement of EEA-motif-associated mechanisms in cellular reprogramming.

Enhanced Bacterial Immunity and Mammalian Genome Editing via RNA-Polymerase-Mediated Dislodging of Cas9 from Double-Strand DNA Breaks

The ability to target the Cas9 nuclease to DNA sequences via Watson-Crick base pairing with a single guide RNA (sgRNA) has provided a dynamic tool for genome editing and an essential component of adaptive immune systems in bacteria. After generating a double-stranded break (DSB), Cas9 remains stably bound to DNA. Here, we show persistent Cas9 binding blocks access to the DSB by repair enzymes, reducing genome editing efficiency. Cas9 can be dislodged by translocating RNA polymerases, but only if the polymerase approaches from one direction toward the Cas9-DSB complex. By exploiting these RNA-polymerase/Cas9 interactions, Cas9 can be conditionally converted into a multi-turnover nuclease, mediating increased mutagenesis frequencies in mammalian cells and enhancing bacterial immunity to bacteriophages. These consequences of a stable Cas9-DSB complex provide insights into the evolution of protospacer adjacent motif (PAM) sequences and a simple method of improving selection of highly active sgRNAs for genome editing.

Class 2 CRISPR-Cas nucleases are programmable genome editing tools with promising applications in human health and disease. However, DNA cleavage at off-target sites that resemble the target sequence is a pervasive problem that remains poorly understood mechanistically. Here, we use quantitative kinetics to dissect the reaction steps of DNA targeting by *Acidaminococcus* sp Cas12a (also known as Cpf1). We show that Cas12a binds DNA tightly in two kinetically separable steps. Protospacer-adjacent motif (PAM) recognition is followed by rate-limiting R-loop propagation, leading to inevitable DNA cleavage of both strands. Despite functionally irreversible binding, Cas12a discriminates strongly against mismatches along most of the DNA target sequence. This result implies substantial reversibility during R-loop formation—a late transition state—and defies common descriptions of a “seed” region. Our results provide a quantitative basis for the DNA cleavage patterns measured *in vivo* and observations of greater reported target specificity for Cas12a than for the Cas9 nuclease.

In vitro–transcribed guide RNAs trigger an innate immune response via the RIG-I pathway

Beeke Wienert, Jiyung Shin, Elena Zelin, Kathleen Pestal, Jacob E. Corn 

Clustered, regularly interspaced, short palindromic repeat (CRISPR)–CRISPR-associated 9 (Cas9) genome editing is revolutionizing fundamental research and has great potential for the treatment of many diseases. While editing of immortalized cell lines has become relatively easy, editing of therapeutically relevant primary cells and tissues can remain challenging. One recent advancement is the delivery of a Cas9 protein and an in vitro–transcribed (IVT) guide RNA (gRNA) as a precomplexed ribonucleoprotein (RNP). This approach allows editing of primary cells such as T cells and hematopoietic stem cells, but the consequences beyond genome editing of introducing foreign Cas9 RNPs into mammalian cells are not fully understood. Here, we show that the IVT gRNAs commonly used by many laboratories for RNP editing trigger a potent innate immune response that is similar to canonical immune-stimulating ligands. IVT gRNAs are recognized in the cytosol through the retinoic acid–inducible gene I (RIG-I) pathway but not the melanoma differentiation–associated gene 5 (MDA5) pathway, thereby triggering a type I interferon response. Removal of the 5′-triphosphate from gRNAs ameliorates inflammatory signaling and prevents the loss of viability associated with genome editing in hematopoietic stem cells. The potential for Cas9 RNP editing to induce a potent antiviral response indicates that care must be taken when designing therapeutic strategies to edit primary cells.

Repair of double-strand breaks induced by CRISPR–Cas9 leads to large deletions and complex rearrangements



Michael Kosicki, Kärt Tomberg & Allan Bradley [✉](#)


Nature Biotechnology | [Download Citation](#) [↓](#)

Abstract

CRISPR–Cas9 is poised to become the gene editing tool of choice in clinical contexts. Thus far, exploration of Cas9-induced genetic alterations has been limited to the immediate vicinity of the target site and distal off-target sequences, leading to the conclusion that CRISPR–Cas9 was reasonably specific. Here we report significant on-target mutagenesis, such as large deletions and more complex genomic rearrangements at the targeted sites in mouse embryonic stem cells, mouse hematopoietic progenitors and a human differentiated cell line. Using long-read sequencing and long-range PCR genotyping, we show that DNA breaks introduced by single-guide RNA/Cas9 frequently resolved into deletions extending over many kilobases. Furthermore, lesions distal to the cut site and crossover events were identified. The observed genomic damage in mitotically active cells caused by CRISPR–Cas9 editing may have pathogenic consequences.

No unexpected CRISPR-Cas9 off-target activity revealed by trio sequencing of gene-edited mice

Vivek Iyer  , Katharina Boroviak , Mark Thomas, Brendan Doe, Laura Riva, Edward Ryder , David J. Adams 

Version 2 

Published: July 9, 2018 • <https://doi.org/10.1371/journal.pgen.1007503>

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References

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Abstract

CRISPR-Cas9 technologies have transformed genome-editing of experimental organisms and have immense therapeutic potential. Despite significant advances in our understanding of the CRISPR-Cas9 system, concerns remain over the potential for off-target effects. Recent studies have addressed these concerns using whole-genome sequencing (WGS) of gene-edited embryos or animals to search for *de novo* mutations (DNMs), which may represent candidate changes introduced by poor editing fidelity. Critically, these studies used strain-matched, but not pedigree-matched controls and thus were unable to reliably distinguish generational or colony-related differences from true DNMs. Here we used a trio design and whole genome sequenced 8 parents and 19 embryos, where 10 of the embryos were mutagenised with well-characterised gRNAs targeting the coat colour Tyrosinase (*Tyr*) locus. Detailed analyses of these whole genome data allowed us to conclude that if CRISPR mutagenesis were causing SNV or indel off-target mutations in treated embryos, then the number of these mutations is not statistically distinguishable from the background rate of DNMs occurring due to other processes.

No off-target mutations in functional genome regions of a CRISPR/Cas9-generated monkey model of muscular dystrophy

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CRISPR/Cas9 is now widely used in biomedical research and has great potential for clinical applications. However, the safety and efficacy of this gene-editing technique are significant issues. Recent reports on mouse models and human cells have raised concerns that off-target mutations could hamper applying the CRISPR technology in patients. The high similarities of nonhuman primates to humans in genome content and organization, genetic diversity, physiology, and cognitive abilities have made these animals ideal experimental models for understanding human diseases and developing therapeutics. Off-target mutations of CRISPR/Cas9 have been analyzed in previous studies of nonhuman primates, but no report has investigated genome-wide off-target effects in living monkeys. Here, we used rhesus monkeys in which a genetic disorder mimicking Duchenne muscular dystrophy had previously been produced with CRISPR/Cas9. Using whole-genome sequencing to comprehensively assess on- and off-target mutations in these animals, we found that CRISPR/Cas9-based gene editing is active on the expected genomic sites without producing off-target modifications in other functional regions of the genome. These findings suggest that the CRISPR/Cas9 technique could be relatively safe and effective in modeling genetic disease in nonhuman primates and in future therapeutic research of human diseases.

Macrophage phenotype and bioenergetics are controlled by oxidized phospholipids identified in lean and obese adipose tissue

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Adipose tissue macrophages (ATMs) adapt their metabolic phenotype either to maintain lean tissue homeostasis or drive inflammation and insulin resistance in obesity. However, the factors in the adipose tissue microenvironment that control ATM phenotypic polarization and bioenergetics remain unknown. We have recently shown that oxidized phospholipids (OxPL) uniquely regulate gene expression and cellular metabolism in *Mox* macrophages, but the presence of the *Mox* phenotype in adipose tissue has not been reported. Here we show, using extracellular flux analysis, that ATMs isolated from lean mice are metabolically inhibited. We identify a unique population of CX3CR1^{neg}/F4/80^{low} ATMs that resemble the *Mox* (Txnrd1⁺HO1⁺) phenotype to be the predominant ATM phenotype in lean adipose tissue. In contrast, ATMs isolated from obese mice had characteristics typical of the *M1/M2* (CD11c⁺CD206⁺) phenotype with highly activated bioenergetics. Quantifying individual OxPL species in the stromal vascular fraction of murine adipose tissue, using targeted liquid chromatography-mass spectrometry, revealed that high fat diet-induced adipose tissue expansion led to a disproportional increase in full-length over truncated OxPL species. In vitro studies showed that macrophages respond to truncated OxPL species by suppressing bioenergetics and up-regulating antioxidant programs, mimicking the *Mox* phenotype of ATMs isolated from lean mice. Conversely, full-length OxPL species induce proinflammatory gene expression and an activated bioenergetic profile that mimics ATMs isolated from obese mice. Together, these data identify a redox-regulatory *Mox* macrophage phenotype to be predominant in lean adipose tissue and demonstrate that individual OxPL species that accumulate in adipose tissue instruct ATMs to adapt their phenotype and bioenergetic profile to either maintain redox homeostasis or to promote inflammation.

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The Carbohydrate-Insulin Model of Obesity: Beyond "Calories In, Calories Out".

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Abstract

Despite intensive research, the causes of the obesity epidemic remain incompletely understood and conventional calorie-restricted diets continue to lack long-term efficacy. According to the carbohydrate-insulin model (CIM) of obesity, recent increases in the consumption of processed, high-glycemic-load carbohydrates produce hormonal changes that promote calorie deposition in adipose tissue, exacerbate hunger, and lower energy expenditure. Basic and genetic research provides mechanistic evidence in support of the CIM. In animals, dietary composition has been clearly demonstrated to affect metabolism and body composition, independently of calorie intake, consistent with CIM predictions. Meta-analyses of behavioral trials report greater weight loss with reduced-glycemic load vs low-fat diets, though these studies characteristically suffer from poor long-term compliance. Feeding studies have lacked the rigor and duration to test the CIM, but the longest such studies tend to show metabolic advantages for low-glycemic load vs low-fat diets. Beyond the type and amount of carbohydrate consumed, the CIM provides a conceptual framework for understanding how many dietary and nondietary exposures might alter hormones, metabolism, and adipocyte biology in ways that could predispose to obesity. Pending definitive studies, the principles of a low-glycemic load diet offer a practical alternative to the conventional focus on dietary fat and calorie restriction.

REVIEW

Next-Generation Machine Learning for Biological Networks

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[Next-Generation Machine Learning for Biological Networks](#)

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Comments

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.