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Scientific News
14th of July 2019
Sven Bulterijs

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“Tegen 2040 zal ons land 3,8 procent van het bruto binnenlands product (bbp) extra aan sociale uitgaven besteden. In geld van vandaag is dat een meeruitgave van bijna 17 miljard euro.”

Vergrijzing kost sociale zekerheid 17 miljard extra tegen 2040

09 juli 2019 11:36

Door de vergrijzing nemen de sociale uitgaven verder toe. ©BELGA

https://www.een.be/op-naar-de-100/kan-dit-geneesmiddel-je-leven-verlengen

Eén > Op naar de 100! > Kan dit geneesmiddel je leven verlengen?

Een aantal bestaande geneesmiddelen zouden een levensverlengend effect hebben terwijl ze daar helemaal niet voor bedoeld zijn. Zo is er het medicijn Metformine, bedoeld voor diabetes type 2 patiënten, dat een levensverlengend effect zou hebben, evengoed op mensen die geen diabetes hebben.

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UNITY Biotechnology Reports Promising Topline Data from Phase 1 First-in-human Study of UBX0101 in Patients with Osteoarthritis of the Knee

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June 18, 2019 07:00 ET | **Source:** Unity Biotechnology, Inc.

Clinical results support senescent cell elimination with UBX0101 as a potential treatment for osteoarthritis

Topline results demonstrate a dose-dependent and clinically meaningful impact on pain

Call with management scheduled for today at 8:00 a.m. EDT

SAN FRANCISCO, June 18, 2019 (GLOBE NEWSWIRE) -- UNITY Biotechnology, Inc. (UNITY) [NASDAQ: UBX], a biotechnology company developing therapeutics to extend healthspan by slowing, halting or reversing diseases of aging, today announced promising results from its first-in-human Phase 1 study of UBX0101 in patients with moderate to severe osteoarthritis (OA) of the knee. The study demonstrated that UBX0101 was safe and well-tolerated. Improvement in several clinical measures, including pain, function, as well as modulation of certain senescence-associated secretory phenotype (SASP) factors and disease-related biomarkers was observed after a single dose of UBX0101.

"This Phase 1 study of UBX0101 is an important first step in exploring the potential of a senolytic approach in the treatment of a range of age-related diseases," said Keith Leonard, chairman and chief executive officer of UNITY. "We believe our novel approach to eliminating senescent cells has the potential to meaningfully impact healthspan."

"New treatments for OA are desperately needed, especially an intervention that targets the biology of the condition that includes cell senescence," said Richard F. Loeser, Jr., M.D., Director, UNC Thurston Arthritis Research Center Herman and Louise Smith Distinguished Professor of Medicine, Division of Rheumatology, Allergy & Immunology. "These exciting data are supportive of this very promising new approach for this chronic painful condition."

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Seattle biotech startup OncoSenX raises $3M to develop tumor-killing therapeutics

BY TAYLOR SOPER on July 8, 2019 at 5:13 pm

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Story updated with comments from Scholz below.

Seattle biotech startup OncoSenX has reeled in $3 million to advance its pipeline of therapeutics that aim to kill cancer cells based on their genetics.

OncoSenX's technology targets solid tumors based on a patented lipid nanoparticle gene delivery system and a highly targeted DNA payload. The company claims that its approach is "a less invasive, more precise intervention" of cancer therapy.

Matthew Scholz. (Matthew Scholz Photo)

OncoSenX is a spinout out of Oisin Biotechnologies, a 5-year-old Seattle company led by veteran biotech entrepreneur Matthew Scholz, who is CEO of OncoSenX. Gary Hudson, a private spaceflight entrepreneur, co-founded Oisin with Scholz and is chairman of OncoSenX.

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"The 2019 class of top drug launches shows the booming of expensive orphan drugs that are based on novel technologies, as well as the undying enthusiasm about the growing immunology market whose opportunity is evident in the world's best-selling drug Humira."

The top 10 drug launches of 2019

by Angus Liu | Jun 24, 2019 12:00pm

Treatments in immunology and for rare genetic diseases are the mainstays of the 2019 class of top drug launches. (Getty/ADragan)

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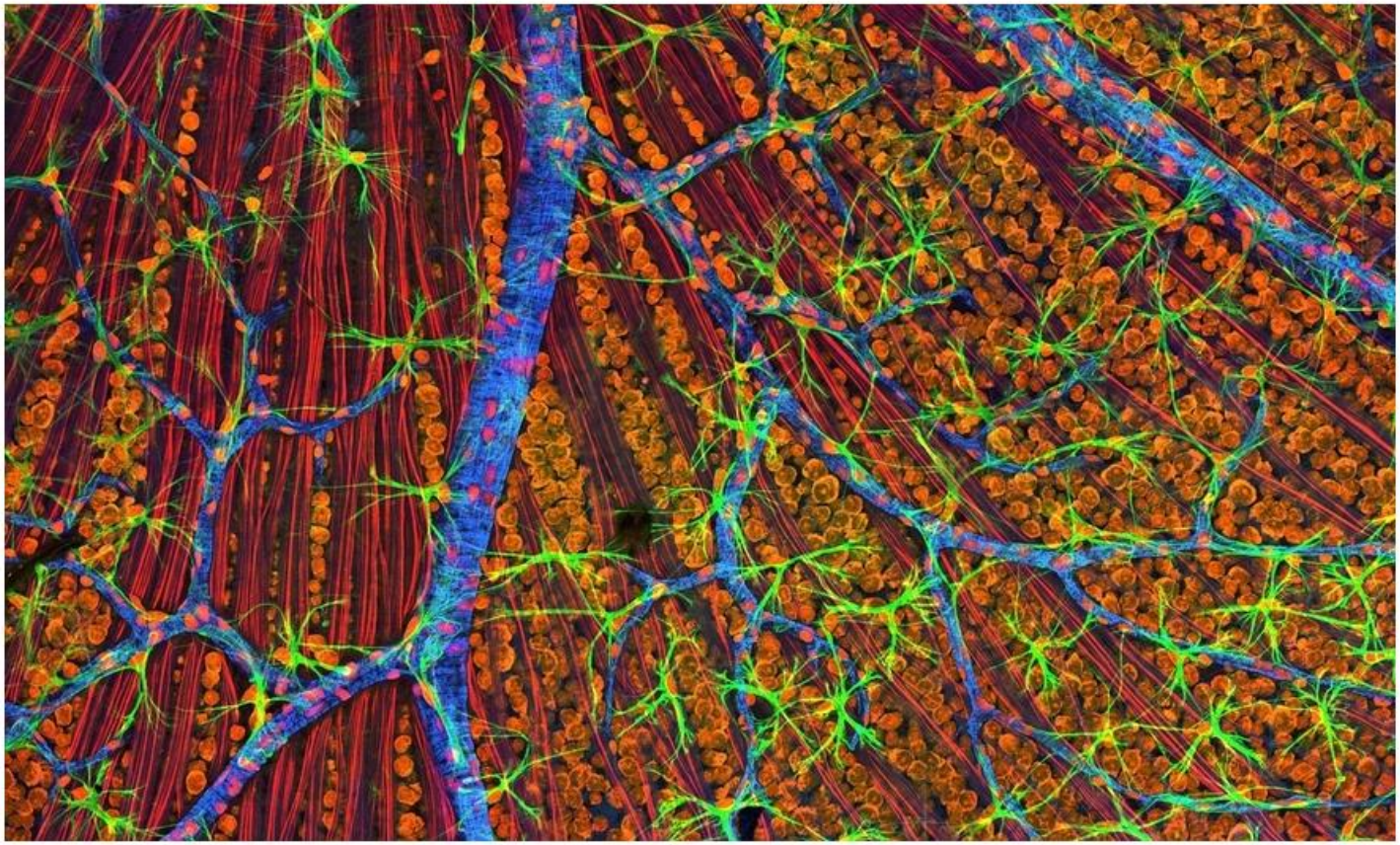
Chan Zuckerberg Initiative awards $68M for cell- and tissue-mapping seed projects

by Conor Hale | Jun 26, 2019 9:25am



While many of the Chan Zuckerberg Initiative-funded projects will focus on mapping out organ systems, others will be developing broader technologies for the undertaking such as proteomic imaging and sequencing of cell interactions. (Pixabay)

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Telomere shortening rate predicts species life span

Kurt Whittemore, Elsa Vera, Eva Martínez-Nevado, Carola Sanpera, and Maria A. Blasco

Telomere shortening to a critical length can trigger aging and shorter life spans in mice and humans by a mechanism that involves induction of a persistent DNA damage response at chromosome ends and loss of cellular viability. However, whether telomere length is a universal determinant of species longevity is not known. To determine whether telomere shortening can be a single parameter to predict species longevities, here we measured in parallel the telomere length of a wide variety of species (birds and mammals) with very different life spans and body sizes, including mouse (*Mus musculus*), goat (*Capra hircus*), Audouin's gull (*Larus audouinii*), reindeer (*Rangifer tarandus*), griffon vulture (*Gyps fulvus*), bottlenose dolphin (*Tursiops truncatus*), American flamingo (*Phoenicopterus ruber*), and Sumatran elephant (*Elephas maximus sumatranus*). We found that the telomere shortening rate, but not the initial telomere length alone, is a powerful predictor of species life span. These results support the notion that critical telomere shortening and the consequent onset of telomeric DNA damage and cellular senescence are a general determinant of species life span.

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Aging (Albany NY). 2019 May 28;11(10):2916-2948. doi: 10.18632/aging.101982.

Telomerase gene therapy ameliorates the effects of neurodegeneration associated to short telomeres in mice.

Whittemore K[1], Derevyanko A[1], Martinez P[1], Serrano R[1], Pumarola M[2,3], Bosch F[4,5], Blasco MA[1].

Author information

Abstract

Neurodegenerative diseases associated with old age such as Alzheimer's disease present major problems for society, and they currently have no cure. The telomere protective caps at the ends of chromosomes shorten with age, and when they become critically short, they can induce a persistent DNA damage response at chromosome ends, triggering secondary cellular responses such as cell death and cellular senescence. Mice and humans with very short telomeres owing to telomerase deficiencies have an earlier onset of pathologies associated with loss of the regenerative capacity of tissues. However, the effects of short telomeres in very low proliferative tissues such as the brain have not been thoroughly investigated. Here, we describe a mouse model of neurodegeneration owing to presence of short telomeres in the brain as the consequence of telomerase deficiency. Interestingly, we find similar signs of neurodegeneration in very old mice as the consequence of physiological mouse aging. Next, we demonstrate that delivery of telomerase gene therapy to the brain of these mice results in amelioration of some of these neurodegeneration phenotypes. These findings suggest that short telomeres contribute to neurodegeneration diseases with aging and that telomerase activation may have a therapeutic value in these diseases.

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Biochim Biophys Acta Proteins Proteom. 2019 Jun 19. pii: S1570-9639(19)30114-1. doi: 10.1016/j.bbapap.2019.06.009. [Epub ahead of print]

Cleavage C-terminal to Asp leads to covalent crosslinking of long-lived human proteins.

Wang Z[1], Friedrich MG[2], Truscott RJW[3], Schey KL[4].

⊕ Author information

Abstract

With age, long-lived proteins in the human body deteriorate, which can have consequences both for aging and disease. The aging process is often associated with the formation of covalently crosslinked proteins. Currently our knowledge of the mechanism of formation of these crosslinks is limited. In this study, proteomics was used to characterize sites of covalent protein-protein crosslinking and identify a novel mechanism of protein-protein crosslinking in the adult human lens. In this mechanism, Lys residues are crosslinked to C-terminal Asp residues that are formed by non-enzymatic protein truncation. Ten different crosslinks were identified in major lens proteins such as αA-crystallin, αB-crystallin and AQP0. Crosslinking in AQP0 increased significantly with age and also increased significantly in cataract lenses compared with normal lenses. Using model peptides, a mechanism of formation of the Lys-Asp crosslink was elucidated. The mechanism involves spontaneous peptide cleavage on the C-terminal side of Asp residues which can take place in the pH range 5-7.4. Cleavage appears to involve attack by the side chain carboxyl group on the adjacent peptide bond, resulting in the formation of a C-terminal Asp anhydride. This anhydride intermediate can then either react with water to form Asp, or with a nucleophile, such as a free amine group to form a crosslink. If an ε-amino group of Lys or an N-terminal amine group attacks the anhydride, a covalent protein-protein crosslink will be formed. This bi-phasic mechanism represents the first report to link two spontaneous events: protein cleavage and crosslinking that are characteristic of long-lived proteins.

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Lysyl oxidase-like 2 depletion is protective in age-associated vascular stiffening

Vascular stiffening and its sequelae are major causes of morbidity and mortality in the elderly. The increasingly accepted concept of “smooth muscle cell (SMC) stiffness syndrome” along with matrix deposition has emerged in vascular biology to account for the mechanical phenotype of arterial aging, but the molecular targets remain elusive. In this study, using an unbiased proteomic analysis, we identified lysyl oxidase-like 2 (LOXL2) as a critical SMC mediator for age-associated vascular stiffening. We tested the hypothesis that loss of LOXL2 function is protective in aging-associated vascular stiffening. We determined that exogenous and endogenous nitric oxide markedly decreased LOXL2 abundance and activity in the extracellular matrix of isolated SMCs and LOXL2 endothelial cells suppress LOXL2 abundance in the aorta. In a longitudinal study, $LOXL2^{+/-}$ mice were protected from age-associated increase in pulse-wave velocity, an index of vascular stiffening, as occurred in littermate wild-type mice. Using isolated aortic segments, we found that LOXL2 mediates vascular stiffening in aging by promoting SMC stiffness, augmented SMC contractility, and vascular matrix deposition. Together, these studies establish LOXL2 as a nodal point for a new therapeutic approach to treat age-associated vascular stiffening.

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Exp Gerontol. 2019 Jul 3:110650. doi: 10.1016/j.exger.2019.110650. [Epub ahead of print]

Aging-induced elevation in circulating complement C1q level is associated with arterial stiffness.

Hasegawa N[1], Fujie S[2], Horii N[3], Uchida M[4], Toyama Y[4], Inoue K[4], Sanada K[4], Hamaoka T[5], Iemitsu M[6].

Author information

Abstract

Inflammatory cytokines such as tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6) are candidate blood biomarkers of cardiovascular disease (CVD). However, no consensus has been reached on the relationships between aging-induced secretion of cytokines and CVD risk. Complement C1q (C1q) secretion increases with aging, and C1q induces proliferation of vascular smooth muscle cells. Therefore, the secretion of C1q with aging may be a risk factor of CVD and reflect arterial stiffening and blood pressures. This study aimed to clarify whether aging-induced increase in serum C1q, TNF-α, and IL-6 levels are associated with arterial stiffness. One hundred twenty-seven healthy subjects participated in this study. Serum C1q, TNF-α, and IL-6 levels and carotid-femoral pulse wave velocity (cfPWV; arterial stiffness index) in middle-aged and older subjects (≥40 years) were significantly increased as compared with those in young subjects (<40 years; $P < 0.05$). The serum C1q, TNF-α, and IL-6 levels positively correlated with cfPWV ($P < 0.05$). Furthermore, C1q level contributed independently to the cfPWV variation after adjustment for 11 confounders. Moreover, serum C1q level is associated with cfPWV regardless of sex, but these relationships with TNF-α or IL-6 differed between sex. Importantly, cfPWV gradually increased from the age of 30 years, with simultaneous increase in circulating C1q level. However, TNF-α and IL-6 levels increased after age 50 years, later than the increase in C1q. These results suggest that serum C1q level may reflect the elevation of arterial stiffness that occurs with advancing age and has a potential as a novel biomarker of arterial stiffness.

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Poly(ADP-Ribose) Links the DNA Damage Response and Biomineralization

Biomineralization of the extracellular matrix is an essential, regulated process. Inappropriate mineralization of bone and the vasculature has devastating effects on patient health, yet an integrated understanding of the chemical and cell biological processes that lead to mineral nucleation remains elusive. Here, we report that biomineralization of bone and the vasculature is associated with extracellular poly(ADP-ribose) synthesized by poly(ADP-ribose) polymerases in response to oxidative and/or DNA damage. We use ultrastructural methods to show poly(ADP-ribose) can form both calcified spherical particles, reminiscent of those found in vascular calcification, and biomimetically calcified collagen fibrils similar to bone. Importantly, inhibition of poly(ADP-ribose) biosynthesis *in vitro* and *in vivo* inhibits biomineralization, suggesting a therapeutic route for the treatment of vascular calcifications. We conclude that poly(ADP-ribose) plays a central chemical role in both pathological and physiological extracellular matrix calcification.

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The mitophagy activator urolithin A is safe and induces a molecular signature of improved mitochondrial and cellular health in humans

Urolithin A (UA) is a natural dietary, microflora-derived metabolite shown to stimulate mitophagy and improve muscle health in old animals and in preclinical models of aging[1]. Here, we report the results of a first-in-human clinical trial in which we administered UA, either as a single dose or as multiple doses over a 4-week period, to healthy, sedentary elderly individuals. We show that UA has a favourable safety profile (primary outcome). UA was bioavailable in plasma at all doses tested, and 4 weeks of treatment with UA at doses of 500 mg and 1,000 mg modulated plasma acylcarnitines and skeletal muscle mitochondrial gene expression in elderly individuals (secondary outcomes). These observed effects on mitochondrial biomarkers show that UA induces a molecular signature of improved mitochondrial and cellular health following regular oral consumption in humans.

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Longevity-related molecular pathways are subject to midlife "switch" in humans

Emerging evidence indicates that molecular aging may follow nonlinear or discontinuous trajectories. Whether this occurs in human neuromuscular tissue, particularly for the noncoding transcriptome, and independent of metabolic and aerobic capacities, is unknown. Applying our novel RNA method to quantify tissue coding and long noncoding RNA (lncRNA), we identified ~800 transcripts tracking with age up to ~60 years in human muscle and brain. In silico analysis demonstrated that this temporary linear "signature" was regulated by drugs, which reduce mortality or extend life span in model organisms, including 24 inhibitors of the IGF-1/PI3K/mTOR pathway that mimicked, and 5 activators that opposed, the signature. We profiled Rapamycin in nondividing primary human myotubes (n = 32 HTA 2.0 arrays) and determined the transcript signature for reactive oxygen species in neurons, confirming that our age signature was largely regulated in the "pro-longevity" direction. Quantitative network modeling demonstrated that age-regulated ncRNA equaled the contribution of protein-coding RNA within structures, but tended to have a lower heritability, implying lncRNA may better reflect environmental influences. Genes ECSIT, UNC13, and SKAP2 contributed to a network that did *not* respond to Rapamycin, and was associated with "neuron apoptotic processes" in protein–protein interaction analysis (FDR = 2.4%). ECSIT links inflammation with the continued age-related downwards trajectory of mitochondrial complex I gene expression (FDR < 0.01%), implying that sustained inhibition of ECSIT may be maladaptive. The present observations link, for the first time, model organism longevity programs with the endogenous but temporary genome-wide responses to aging in humans, revealing a pattern that may ultimately underpin personalized rates of health span.

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Extracellular Vesicle-Contained eNAMPT Delays Aging and Extends Lifespan in Mice

Mitsukuni Yoshida [1, 6], Akiko Satoh [7], Jonathan B. Lin [2, 6], Kathryn F. Mills [1], Yo Sasaki [3], Nicholas Rensing [4], Michael Wong [4], Rajendra S. Apte [1, 2, 5], Shin-ichiro Imai [1, 5, 8, 9]

Aging is a significant risk factor for impaired tissue functions and chronic diseases. Age-associated decline in systemic NAD^+ availability plays a critical role in regulating the aging process across many species. Here, we show that the circulating levels of extracellular nicotinamide phosphoribosyltransferase (eNAMPT) significantly decline with age in mice and humans. Increasing circulating eNAMPT levels in aged mice by adipose-tissue-specific overexpression of NAMPT increases NAD^+ levels in multiple tissues, thereby enhancing their functions and extending healthspan in female mice. Interestingly, eNAMPT is carried in extracellular vesicles (EVs) through systemic circulation in mice and humans. EV-contained eNAMPT is internalized into cells and enhances NAD^+ biosynthesis. Supplementing eNAMPT-containing EVs isolated from young mice significantly improves wheel-running activity and extends lifespan in aged mice. Our findings have revealed a novel EV-mediated delivery mechanism for eNAMPT, which promotes systemic NAD^+ biosynthesis and counteracts aging, suggesting a potential avenue for anti-aging intervention in humans.

J Invest Dermatol. 2019 Jun 17. pii: S0022-202X(19)31754-3. doi: 10.1016/j.jid.2019.05.015. [Epub ahead of print]

Extracellular vesicles in human skin: cross-talk from senescent fibroblasts to keratinocytes by miRNAs.

Terlecki-Zaniewicz L[1], Pils V[1], Bobbili MR[2], Lämmermann I[1], Perrotta I[3], Grillenberger T[1], Schwestka J[1], Weiß K[1], Pum D[4], Arcalis E[5], Schwingenschuh S[6], Birngruber T[6], Brandstetter M[7], Heuser T[7], Schosserer M[2], Morizot F[8], Mildner M[9], Stöger E[5], Tschachler E[9], Weinmüllner R[1], Gruber F[10], Grillari J[11].

⊕ Author information

Abstract

Extracellular vesicles (EVs) and their miRNA cargo are intercellular communicators transmitting their pleiotropic messages between different cell types, tissues and body fluids. Recently, they have been reported to contribute to skin homeostasis and were identified as to our knowledge previously unreported members of the senescence-associated secretory phenotype (SASP) of human dermal fibroblasts. However, the role of EV-miRNAs in paracrine signaling during skin aging is yet unclear. Here we provide evidence for the existence of small EVs in human skin and dermal interstitial fluid using dermal open flow microperfusion and show that EVs and miRNAs are transferred from dermal fibroblasts to epidermal keratinocytes in 2D cell culture, as well as in human skin equivalents. We further show that the transient presence of senescent fibroblast derived small EVs accelerates scratch closure of epidermal keratinocytes, while long-term incubation impairs keratinocyte differentiation in vitro. Finally, we identify vesicular miR-23a-3p, highly secreted by senescent fibroblasts, as one contributor of the EV mediated effect on keratinocytes in in vitro wound healing assays. To summarize, our findings support the current view that EVs and their miRNA cargo are members of the SASP and thus regulators of human skin homeostasis during aging.

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Senescent cells evade immune clearance via HLA-E-mediated NK and CD8$^+$ T cell inhibition

Senescent cells accumulate in human tissues during ageing and contribute to age-related pathologies. The mechanisms responsible for their accumulation are unclear. Here we show that senescent dermal fibroblasts express the non-classical MHC molecule HLA-E, which interacts with the inhibitory receptor NKG2A expressed by NK and highly differentiated CD8$^+$ T cells to inhibit immune responses against senescent cells. HLA-E expression is induced by senescence-associated secretary phenotype-related pro-inflammatory cytokines, and is regulated by p38 MAP kinase signalling in vitro. Consistently, HLA-E expression is increased on senescent cells in human skin sections from old individuals, when compared with those from young, and in human melanocytic nevi relative to normal skin. Lastly, blocking the interaction between HLA-E and NKG2A boosts immune responses against senescent cells in vitro. We thus propose that increased HLA-E expression contributes to persistence of senescent cells in tissues, thereby suggesting a new strategy for eliminating senescent cells during ageing.

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Interplay between Follistatin, Activin A, and BMP4 Signaling Regulates Postnatal Thymic Epithelial Progenitor Cell Differentiation during Aging

A key feature of immune functional impairment with age is the progressive involution of thymic tissue responsible for naive T cell production. In this study, we identify two major phases of thymic epithelial cell (TEC) loss during aging: a block in mature TEC differentiation from the pool of immature precursors, occurring at the onset of puberty, followed by impaired bipotent TEC progenitor differentiation and depletion of Sca-1^{lo} cTEC and mTEC lineage-specific precursors. We reveal that an increase in follistatin production by aging TECs contributes to their own demise. TEC loss occurs primarily through the antagonism of activin A signaling, which we show is required for TEC maturation and acts in dissonance to BMP4, which promotes the maintenance of TEC progenitors. These results support a model in which an imbalance of activin A and BMP4 signaling underpins the degeneration of postnatal TEC maintenance during aging, and its reversal enables the transient replenishment of mature TECs.

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Acceleration of β Cell Aging Determines Diabetes and Senolysis Improves Disease Outcomes

Type 2 diabetes (T2D) is an age-related disease. Although changes in function and proliferation of aged β cells resemble those preceding the development of diabetes, the contribution of β cell aging and senescence remains unclear. We generated a β cell senescence signature and found that insulin resistance accelerates β cell senescence leading to loss of function and cellular identity and worsening metabolic profile. Senolysis (removal of senescent cells), using either a transgenic INK-ATTAC model or oral ABT263, improved glucose metabolism and β cell function while decreasing expression of markers of aging, senescence, and senescence-associated secretory profile (SASP). Beneficial effects of senolysis were observed in an aging model as well as with insulin resistance induced both pharmacologically (S961) and physiologically (high-fat diet). Human senescent β cells also responded to senolysis, establishing the foundation for translation. These novel findings lay the framework to pursue senolysis of β cells as a preventive and alleviating strategy for T2D.

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Transneuronal Propagation of Pathologic α-Synuclein from the Gut to the Brain Models Parkinson's Disease

Analysis of human pathology led Braak to postulate that α-synuclein (α-syn) pathology could spread from the gut to brain via the vagus nerve. Here, we test this postulate by assessing α-synucleinopathy in the brain in a novel gut-to-brain α-syn transmission mouse model, where pathological α-syn preformed fibrils were injected into the duodenal and pyloric muscularis layer. Spread of pathologic α-syn in brain, as assessed by phosphorylation of serine 129 of α-syn, was observed first in the dorsal motor nucleus, then in caudal portions of the hindbrain, including the locus coeruleus, and much later in basolateral amygdala, dorsal raphe nucleus, and the substantia nigra pars compacta. Moreover, loss of dopaminergic neurons and motor and non-motor symptoms were observed in a similar temporal manner. Truncal vagotomy and α-syn deficiency prevented the gut-to-brain spread of α-synucleinopathy and associated neurodegeneration and behavioral deficits. This study supports the Braak hypothesis in the etiology of idiopathic Parkinson's disease (PD).

ACS Chem Biol. 2019 Jun 27. doi: 10.1021/acschembio.9b00354. [Epub ahead of print]

Fast Fluorescence Lifetime Imaging Reveals the Aggregation Processes of α-Synuclein and Polyglutamine in Aging Caenorhabditis elegans.

Laine RF[1], Sinnige T[2], Ma KY[2], Haack AJ[1,3], Poudel C[1], Gaida P[1], Curry N[1], Perni M[2], Nollen EAA[4], Dobson CM[2], Vendruscolo M[2], Kaminski Schierle GS[3], Kaminski CF[1].

Author information

Abstract

The nematode worm Caenorhabditis elegans has emerged as an important model organism in the study of the molecular mechanisms of protein misfolding diseases associated with amyloid formation because of its small size, ease of genetic manipulation, and optical transparency. Obtaining a reliable and quantitative read-out of protein aggregation in this system, however, remains a challenge. To address this problem, we here present a fast time-gated fluorescence lifetime imaging (TG-FLIM) method and show that it provides functional insights into the process of protein aggregation in living animals by enabling the rapid characterization of different types of aggregates. Specifically, in longitudinal studies of C. elegans models of Parkinson's and Huntington's diseases, we observed marked differences in the aggregation kinetics and the nature of the protein inclusions formed by α-synuclein and polyglutamine. In particular, we found that α-synuclein inclusions do not display amyloid-like features until late in the life of the worms, whereas polyglutamine forms amyloid characteristics rapidly in early adulthood. Furthermore, we show that the TG-FLIM method is capable of imaging live and non-anaesthetized worms moving in specially designed agarose microchambers. Taken together, our results show that the TG-FLIM method enables high-throughput functional imaging of living C. elegans that can be used to study in vivo mechanisms of protein aggregation and that has the potential to aid the search for therapeutic modifiers of protein aggregation and toxicity.

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Hydrogen Peroxide Modifies Aβ–Membrane Interactions with Implications for $A\beta_{40}$ Aggregation

Albert W. PilkingtonIV, Gregory C. Donohoe, Novruz G. Akhmedov, Timothy Ferrebee, Stephen J. Valentine and Justin Legleiter*

Alzheimer's disease (AD) is pathologically characterized by the formation of extracellular senile plaques, predominately comprised of aggregated β-amyloid (Aβ), deposited in the brain. Aβ aggregation can result in a myriad of distinct aggregate species, from soluble oligomers to insoluble fibrils. Aβ strongly interacts with membranes, which can be linked to a variety of potential toxic mechanisms associated with AD. Oxidative damage accompanies the formation of Aβ aggregates, with a 10–50% proportion of Aβ aggregates being oxidized in vivo. Hydrogen peroxide (H_2O_2) is a reactive oxygen species implicated in a number of neurodegenerative diseases. Recent evidence has demonstrated that the H_2O_2 concentration fluctuates rapidly in the brain, resulting in large concentration spikes, especially in the synaptic cleft. Here, the impact of environmental H_2O_2 on Aβ aggregation in the presence and absence of lipid membranes is investigated. $A\beta_{40}$ was exposed to H_2O_2, resulting in the selective oxidation of methionine 35 (Met35) to produce $A\beta_{40}$Met35[O]. While oxidation mildly reduced the rate of Aβ aggregation and produced a distinct fibril morphology at high H_2O_2 concentrations, H_2O_2 had a much more pronounced impact on Aβ aggregation in the presence of total brain lipid extract vesicles. The impact of H_2O_2 on Aβ aggregation in the presence of lipids was associated with a reduced affinity of Aβ for the vesicle surface. However, this reduced vesicle affinity was predominately associated with lipid peroxidation rather than Aβ oxidation.

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Brains of rhesus monkeys display Aβ deposits and glial pathology while lacking Aβ dimers and other Alzheimer's pathologies

Cerebral amyloid beta (Aβ) deposits are the main early pathology of Alzheimer's disease (AD). However, abundant Aβ deposits also occur spontaneously in the brains of many healthy people who are free of AD with advancing aging. A crucial unanswered question in AD prevention is why AD does not develop in some elderly people, despite the presence of Aβ deposits. The answer may lie in the composition of Aβ oligomer isoforms in the Aβ deposits of healthy brains, which are different from AD brains. However, which Aβ oligomer triggers the transformation from aging to AD pathogenesis is still under debate. Some researchers insist that the Aβ 12-mer causes AD pathology, while others suggest that the Aβ dimer is the crucial molecule in AD pathology. Aged rhesus monkeys spontaneously develop Aβ deposits in the brain with striking similarities to those of aged humans. Thus, rhesus monkeys are an ideal natural model to study the composition of Aβ oligomer isoforms and their downstream effects on AD pathology. In this study, we found that Aβ deposits in aged monkey brains included 3-mer, 5-mer, 9-mer, 10-mer, and 12-mer oligomers, but not 2-mer oligomers. The Aβ deposits, which were devoid of Aβ dimers, induced glial pathology (microgliosis, abnormal microglia morphology, and astrocytosis), but not the subsequent downstream pathologies of AD, including Tau pathology, neurodegeneration, and synapse loss. Our results indicate that the Aβ dimer plays an important role in AD pathogenesis. Thus, targeting the Aβ dimer is a promising strategy for preventing AD.

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Nicotinamide riboside augments the human skeletal muscle NAD+ metabolome and induces transcriptomic and anti-inflammatory signatures in aged subjects: a placebo-controlled, randomized trial

NAD+ is modulated by conditions of metabolic stress and has been reported to decline with aging, but human data are sparse. Nicotinamide riboside (NR) supplementation ameliorates metabolic dysfunction in rodents. We aimed to establish whether oral NR supplementation in aged participants can increase the skeletal muscle NAD+ metabolome, and questioned if tissue NAD+ levels are depressed with aging. We supplemented 12 aged men with NR 1g per day for 21-days in a placebo-controlled, randomized, double-blind, crossover trial. Targeted metabolomics showed that NR elevated the muscle NAD+ metabolome, evident by increased nicotinic acid adenine dinucleotide and nicotinamide clearance products. Muscle RNA sequencing revealed NR-mediated downregulation of energy metabolism and mitochondria pathways. NR also depressed levels of circulating inflammatory cytokines. In an additional study, 31P magnetic resonance spectroscopy-based NAD+ measurement in muscle and brain showed no difference between young and aged individuals. Our data establish that oral NR is available to aged human muscle and identify anti-inflammatory effects of NR, while suggesting that NAD+ decline is not associated with chronological aging per se in human muscle or brain. Clinical Trial Registration ID #NCT02950441.

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Nucleic Acids Res. 2019 Jun 21. pii: gkz519. doi: 10.1093/nar/gkz519. [Epub ahead of print]

SIRT7 mediates L1 elements transcriptional repression and their association with the nuclear lamina.

Vazquez BN[1,2], Thackray JK[1], Simonet NG[3], Chahar S[1,4], Kane-Goldsmith N[1], Newkirk SJ[5], Lee S[5], Xing J[1], Verzi MP[1], An W[5], Vaquero A[2,3], Tischfield JA[1], Serrano L[1].

⊕ Author information

Abstract

Long interspersed elements-1 (LINE-1, L1) are retrotransposons that hold the capacity of self-propagation in the genome with potential mutagenic outcomes. How somatic cells restrict L1 activity and how this process becomes dysfunctional during aging and in cancer cells is poorly understood. L1s are enriched at lamin-associated domains, heterochromatic regions of the nuclear periphery. Whether this association is necessary for their repression has been elusive. Here we show that the sirtuin family member SIRT7 participates in the epigenetic transcriptional repression of L1 genome-wide in both mouse and human cells. SIRT7 depletion leads to increased L1 expression and retrotransposition. Mechanistically, we identify a novel interplay between SIRT7 and Lamin A/C in L1 repression. Our results demonstrate that SIRT7-mediated H3K18 deacetylation regulates L1 expression and promotes L1 association with elements of the nuclear lamina. The failure of such activity might contribute to the observed genome instability and compromised viability in SIRT7 knockout mice. Overall, our results reveal a novel function of SIRT7 on chromatin organization by mediating the anchoring of L1 to the nuclear envelope, and a new functional link of the nuclear lamina with transcriptional repression.

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Cellular response to moderate chromatin architectural defects promotes longevity

Ruofan Yu[1], Luyang Sun[1], Yu Sun[1], Xin Han[2,*], Lidong Qin[2] and Weiwei Dang[1,†]

Abstract

Changes in chromatin organization occur during aging. Overexpression of histones partially alleviates these changes and promotes longevity. We report that deletion of the histone H3-H4 minor locus *HHT1-HHF1* extended the replicative life span of *Saccharomyces cerevisiae*. This longevity effect was mediated through TOR signaling inhibition. We present evidence for evolutionarily conserved transcriptional and phenotypic responses to defects in chromatin structure, collectively termed the chromatin architectural defect (CAD) response. Promoters of the CAD response genes were sensitive to histone dosage, with *HHT1-HHF1* deletion, nucleosome occupancy was reduced at these promoters allowing transcriptional activation induced by stress response transcription factors Msn2 and Gis1, both of which were required for the life-span extension of *hht1-hhf1*Δ. Therefore, we conclude that the CAD response induced by moderate chromatin defects promotes longevity.

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Longitudinal comparative transcriptomics reveals unique mechanisms underlying extended healthspan in bats

Bats are the longest-lived mammals, given their body size. However, the underlying molecular mechanisms of their extended healthspans are poorly understood. To address this question we carried out an eight-year longitudinal study of ageing in long-lived bats (*Myotis myotis*). We deep-sequenced ~1.7 trillion base pairs of RNA from 150 blood samples collected from known aged bats to ascertain the age-related transcriptomic shifts and potential microRNA-directed regulation that occurred. We also compared ageing transcriptomic profiles between bats and other mammals by analysis of 298 longitudinal RNA sequencing datasets. Bats did not show the same transcriptomic changes with age as commonly observed in humans and other mammals, but rather exhibited a unique, age-related gene expression pattern associated with DNA repair, autophagy, immunity and tumour suppression that may drive their extended healthspans. We show that bats have naturally evolved transcriptomic signatures that are known to extend lifespan in model organisms, and identify novel genes not yet implicated in healthy ageing. We further show that bats' longevity profiles are partially regulated by microRNA, thus providing novel regulatory targets and pathways for future ageing intervention studies. These results further disentangle the ageing process by highlighting which ageing pathways contribute most to healthy ageing in mammals.

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New Trend in Old-Age Mortality: Gompertzialization of Mortality Trajectory

Gavrilov L.A. · Gavrilova N.S.

There is great interest among gerontologists, demographers, and actuaries in the question concerning the limits to human longevity. Attempts at getting answers to this important question have stimulated many studies on late-life mortality trajectories, often with opposing conclusions. One group of researchers believes that mortality stops growing with age at extreme old ages, and that hence there is no fixed limit to the human life span. Other studies found that mortality continues to grow with age up to extreme old ages. Our study suggests a possible solution to this controversy. We found that mortality deceleration is best observed when older, less accurate life span data are analyzed, while in the case of more recent and reliable data there is a persistent mortality growth with age. We compared the performance (goodness of fit) of two competing mortality models – the Gompertz model and the Kannisto ("mortality deceleration") model – at ages of 80–105 years using data for 1880–1899 single-year birth cohorts of US men and women. The mortality modeling approach suggests a transition from mortality deceleration to the Gompertzian mortality pattern over time for both men and women. These results are consistent with the hypothesis about disappearing mortality deceleration over time due to improvement in the accuracy of age reporting. In the case of more recent data, mortality continues to grow with age even at very old ages. This observation may lead to more conservative estimates of future human longevity records.

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Are We Approaching a Biological Limit to Human Longevity?

Gavrilova NS[1], Gavrilov LA[1].

⊕ Author information

Abstract

Until recently human longevity records continued to grow in history, with no indication of approaching a hypothetical longevity limit. Also, earlier studies found that age-specific death rates cease to increase at advanced ages (mortality plateau) suggesting the absence of fixed limit to longevity too. In this study we re-examine both claims with more recent and reliable data on supercentenarians (persons aged 110 years and over). We found that despite a dramatic historical increase in the number of supercentenarians, further growth of human longevity records in subsequent birth cohorts slowed down significantly and almost stopped for those born after 1879. We also found an exponential acceleration of age-specific death rates for persons older than 113 years in more recent data. Slowing down the historical progress in maximum reported age at death and accelerated growth of age-specific death rates after age 113 years in recent birth cohorts may indicate the need for more conservative estimates for future longevity records unless a scientific breakthrough in delaying aging would happen. The hypothesis of approaching a biological limit to human longevity has received some empirical support and it deserves further study and testing.

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2 years of calorie restriction and cardiometabolic risk (CALERIE): exploratory outcomes of a multicentre, phase 2, randomised controlled trial

Methods

CALERIE was a phase 2, multicentre, randomised controlled trial in young and middle-aged (21–50 years), healthy non-obese (BMI 22·0–27·9 kg/m ^{2}) men and women done in three clinical centres in the USA. Participants were randomly assigned (2:1) to a 25% calorie restriction diet or an ad libitum control diet. Exploratory cardiometabolic risk factor responses to a prescribed 25% calorie restriction diet for 2 years were evaluated (systolic, diastolic, and mean blood pressure; plasma lipids; high-sensitivity C-reactive protein; metabolic syndrome score; and glucose homoeostasis measures of fasting insulin, glucose, insulin resistance, and 2-h glucose, area-under-the curve for glucose, and insulin from an oral glucose tolerance test) analysed in the intention-to-treat population. This study is registered with ClinicalTrials.gov, number NCT00427193.

Findings

From May 8, 2007, to Feb 26, 2010, of 238 participants that were assessed, 218 were randomly assigned to and started a 25% calorie restriction diet (n=143, 66%) or an ad libitum control diet (n=75, 34%). Individuals in the calorie restriction group achieved a mean reduction in calorie intake of 11·9% (SE 0·7; from 2467 kcal to 2170 kcal) versus 0·8% (1·0) in the control group, and a sustained mean weight reduction of 7·5 kg (SE 0·4) versus an increase of 0·1 kg (0·5) in the control group, of which 71% (mean change in fat mass 5·3 kg [SE 0·3] divided by mean change in weight 7·5 kg [0·4]) was fat mass loss. Calorie restriction caused a persistent and significant reduction from baseline to 2 years of all measured conventional cardiometabolic risk factors, including change scores for LDL-cholesterol ($p<0·0001$), total cholesterol to HDL-cholesterol ratio ($p<0·0001$), and systolic ($p<0·0011$) and diastolic ($p<0·0001$) blood pressure. In addition, calorie restriction resulted in a significant improvement at 2 years in C-reactive protein ($p=0·012$), insulin sensitivity index ($p<0·0001$), and metabolic syndrome score ($p<0·0001$) relative to control. A sensitivity analysis revealed the responses to be robust after controlling for relative weight loss changes.

Interpretation

2 years of moderate calorie restriction significantly reduced multiple cardiometabolic risk factors in young, non-obese adults. These findings suggest the potential for a substantial advantage for cardiovascular health of practicing moderate calorie restriction in young and middle-aged healthy individuals, and they offer promise for pronounced long-term population health benefits.

REVIEWS/COMMENTS/ METHODS/EDITORIALS

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From discoveries in ageing research to therapeutics for healthy ageing

Judith Campisi[1], Pankaj Kapahi[1], Gordon J. Lithgow[1], Simon Melov[1], John C. Newman[1] & Eric Verdin[1]*

For several decades, understanding ageing and the processes that limit lifespan have challenged biologists. Thirty years ago, the biology of ageing gained unprecedented scientific credibility through the identification of gene variants that extend the lifespan of multicellular model organisms. Here we summarize the milestones that mark this scientific triumph, discuss different ageing pathways and processes, and suggest that ageing research is entering a new era that has unique medical, commercial and societal implications. We argue that this era marks an inflection point, not only in ageing research but also for all biological research that affects the human healthspan.

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Towards a unified mechanistic theory of aging.

Barja G[1].

Author information

Abstract

A large amount of the longevity-modulating genes discovered during the last two decades are highly conserved during evolution from yeast and invertebrates to mammals. Many different kinds of evidence converge in the concept that life extending manipulations like the dietary restrictions or rapamycin signal the nucleus specifically changing gene expression to increase longevity. The response of the cell aging regulation system is to change the level of activity of many different aging effectors to modulate longevity. Aging effectors include mitROS production, lipid unsaturation, autophagy, mitochondrial DNA repair and possibly others like apoptosis, proteostasis, or telomere shortening, corresponding to different classic theories of aging. The constitutive spontaneous activity of this aging regulating system, likely including epigenetics, can also explain species longevity. The aging regulating system reconciles the previously considered independent theories of aging bringing them together into a single unified theory of aging.

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FEBS Lett. 2019 Jun 14. doi: 10.1002/1873-3468.13483. [Epub ahead of print]

Mechanisms of cellular rejuvenation.

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Author information

Abstract

Aging leads to changes on an organismal but also cellular level. However, the exact mechanisms of cellular aging in mammals remain poorly understood and the identity and functional role of aging factors, some of which have previously been defined in model organisms such as Saccharomyces cerevisiae, remain elusive. Remarkably, during cellular reprogramming most if not all aging hallmarks are erased, offering a novel entry point to study aging and rejuvenation on a cellular level. On the other hand, direct reprogramming of old cells into cells of a different fate preserves many aging signs. Therefore, investigating the process of reprogramming and comparing it to direct reprogramming may yield novel insights about the clearing of aging factors, which is the basis of rejuvenation. Here, we discuss how reprogramming might lead to rejuvenation of a cell, an organ, or even the whole organism.

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Deep Aging Clocks: The Emergence of AI-Based Biomarkers of Aging and Longevity

First published in 2016, predictors of chronological and biological age developed using deep learning (DL) are rapidly gaining popularity in the aging research community. These deep aging clocks can be used in a broad range of applications in the pharmaceutical industry, spanning target identification, drug discovery, data economics, and synthetic patient data generation. We provide here a brief overview of recent advances in this important subset, or perhaps superset, of aging clocks that have been developed using artificial intelligence (AI).

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Paradoxical lucidity: A potential paradigm shift for the neurobiology and treatment of severe dementias

George A. Mashour[a,*], [1], Lori Frank[b,1], Alexander Batthyany[c], Ann Marie Kolanowski[d], Michael Nahm[e], Dena Schulman-Green[f], Bruce Greyson[g], Serguei Pakhomov[h], Jason Karlawish[i,j,k], Raj C. Shah[l]

Unexpected cognitive lucidity and communication in patients with severe dementias, especially around the time of death, have been observed and reported anecdotally. Here, we review what is known about this phenomenon, related phenomena that provide insight into potential mechanisms, ethical implications, and methodologic considerations for systematic investigation. We conclude that paradoxical lucidity, if systematically confirmed, challenges current assumptions and highlights the possibility of network-level return of cognitive function in cases of severe dementias, which can provide insight into both underlying neurobiology and future therapeutic possibilities.

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The chemistry of senescence

Beatriz Lozano-Torres, Alejandra Estepa-Fernández, Miguel Rovira, Mar Orzáez ✉, Manuel Serrano ✉, Ramón Martínez-Máñez ✉ & Félix Sancenón

Senescence is a state of permanent cell cycle arrest. Cellular senescence can promote tissue remodelling but can negatively affect regenerative capacities of tissues and contribute to inflammation and the progression of cancer and ageing-related diseases. This Review highlights the chemical characteristics of senescence and how we can target senescent cells with small molecules to induce senescence in hyperproliferative tissues. Alternatively, these small molecules can also be administered to inhibit senescence or eliminate senescent cells as the basis of a promising strategy to treat ageing-related diseases. We also describe advances in detecting senescence in in vitro and in vivo models, such that we can evaluate response to treatments intended to induce or eliminate senescent cells.

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Unmasking senescence: context-dependent effects of SASP in cancer

Douglas V. Faget, Qihao Ren & Sheila A. Stewart

Cellular senescence plays a critical role in tumorigenesis. Once thought of as a tissue culture artefact by some researchers, senescence is now a major field of study. Although there are common molecular mechanisms that enforce the growth arrest that characterizes the phenotype, the impact of senescence is varied and can, in some instances, have opposite effects on tumorigenesis. It has become clearer that the cell of origin and the tissue in question dictate the impact of senescence on tumorigenesis. In this Review, we unravel this complexity by focusing on how senescence impacts tumorigenesis when it arises within incipient tumour cells versus stromal cells, and how these roles can change in different stages of disease progression. In addition, we highlight the diversity of the senescent phenotype and its functional output beyond growth arrest: the senescence-associated secretory phenotype (SASP). Fortunately, a number of new genetic and pharmacologic tools have been developed that are now allowing the senescence phenotype to be parsed further.

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Regulation of Survival Networks in Senescent Cells: From Mechanisms to Interventions

Abel Soto-Gamez [1, 2], Wim J. Quax [1], Marco Demaria [2]

Cellular senescence is a state of stable cell cycle arrest arising in response to DNA and mitochondrial damages. Senescent cells undergo morphological, structural and functional changes that are influenced by a number of variables, including time, stress, tissue, and cell type. The heterogeneity of the senescent phenotype is exemplified by the many biological properties that senescent cells can cover. The advent of innovative model organisms has demonstrated a functional role of senescent cells during embryogenesis, tissue remodeling, tumorigenesis and aging. Importantly, prolonged and aberrant persistence of senescent cells is often associated with tissue dysfunction and pathology, and is partially the consequence of mechanisms that enhance survival and resistance to cell death. Here, we describe the main molecular players involved in promoting survival of senescent cells, with particular emphasis on the regulation of senescence-associated anti-apoptotic pathways. We discuss the consequences these pathways have in providing resistance to intrinsic and extrinsic pro-apoptotic signals. Finally, we highlight the importance of these pathways in the development of targets for senolytic interventions.

Coron Artery Dis. 2019 Jun 17. doi: 10.1097/MCA.0000000000000769. [Epub ahead of print]

Coronary artery tortuosity: a narrative review.

Kahe F[1], Sharfaei S, Pitliya A, Jafarizade M, Seifirad S, Habibi S, Chi G.

Author information

Abstract

Coronary artery tortuosity (CAT) is a prevalent angiographic finding commonly associated with aging, hypertension, atherosclerosis and other conditions. Preliminary evidence suggests that degradation of elastin, a key component of extracellular matrix in the vascular wall, may be responsible for the development of CAT. The clinical significance of CAT should be considered in several aspects. First, coronary flow alteration associated with CAT may result in myocardial ischemia owing to reduced perfusion pressure distal to the tortuous segment. Second, increased and oscillatory shear stress in the tortuous vessel may promote atherosclerotic plaque formation and acute coronary syndrome. Third, as one of the criteria for coronary lesion complexity, the presence of severe tortuosity proximal to the culprit lesion may pose a challenge to wiring and stent or balloon delivery, thereby increasing the risk of periprocedural complications. Last, the presence of CAT may serve as a diagnostic clue of concurrent vasculopathy such as fibromuscular dysplasia or spontaneous coronary artery dissection. In general, CAT represents a benign entity that does not require specific treatment or intervention. Further research is warranted to elucidate the pathogenesis and prognostic effect of coronary tortuosity.

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The role of elastin-derived peptides in human physiology and diseases

Aurélie Le Page [a], Abdelouahed Khalil [a], Patrick Vermette [a, b], Eric H. Frost [c], Anis Larbi [d, e], Jacek M. Witkowski [f], Tamas Fulop [a]

Once considered as inert, the extracellular matrix recently revealed to be biologically active. Elastin is one of the most important components of the extracellular matrix. Many vital organs including arteries, lungs and skin contain high amounts of elastin to assure their correct function. Physiologically, the organism contains a determined quantity of elastin from the early development which may remain physiologically constant due to its very long half-life and very low turnover. Taking into consideration the continuously ongoing challenges during life, there is a physiological degradation of elastin into elastin-derived peptides which is accentuated in several disease states such as obstructive pulmonary diseases, atherosclerosis and aortic aneurysm. These elastin-derived peptides have been shown to have various biological effects mediated through their interaction with their cognate receptor called elastin receptor complex eliciting several signal transduction pathways. In this review, we will describe the production and the biological effects of elastin-derived peptides in physiology and pathology.

OTHER RESEARCH

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Whole-animal connectomes of both *Caenorhabditis elegans* sexes

Steven J. Cook, Travis A. Jarrell, Christopher A. Brittin, Yi Wang, Adam E. Bloniarz, Maksim A. Yakovlev, Ken C. Q. Nguyen, Leo T.-H. Tang, Emily A. Bayer, Janet S. Duerr, Hannes E. Bülow, Oliver Hobert, David H. Hall & Scott W. Emmons

Nature **571**, 63–71 (2019) | Download Citation

Abstract

Knowledge of connectivity in the nervous system is essential to understanding its function. Here we describe connectomes for both adult sexes of the nematode *Caenorhabditis elegans*, an important model organism for neuroscience research. We present quantitative connectivity matrices that encompass all connections from sensory input to end-organ output across the entire animal, information that is necessary to model behaviour. Serial electron microscopy reconstructions that are based on the analysis of both new and previously published electron micrographs update previous results and include data on the male head. The nervous system differs between sexes at multiple levels. Several sex-shared neurons that function in circuits for sexual behaviour are sexually dimorphic in structure and connectivity. Inputs from sex-specific circuitry to central circuitry reveal points at which sexual and non-sexual pathways converge. In sex-shared central pathways, a substantial number of connections differ in strength between the sexes. Quantitative connectomes that include all connections serve as the basis for understanding how complex, adaptive behavior is generated.

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Transposon-encoded CRISPR–Cas systems direct RNA-guided DNA integration

Sanne E. Klompe, Phuc L. H. Vo, Tyler S. Halpin-Healy & Samuel H. Sternberg

Nature **571**, 219–225 (2019) | Download Citation

Abstract

Conventional CRISPR–Cas systems maintain genomic integrity by leveraging guide RNAs for the nuclease-dependent degradation of mobile genetic elements, including plasmids and viruses. Here we describe a notable inversion of this paradigm, in which bacterial Tn7-like transposons have co-opted nuclease-deficient CRISPR–Cas systems to catalyse RNA-guided integration of mobile genetic elements into the genome. Programmable transposition of *Vibrio cholerae* Tn6677 in *Escherichia coli* requires CRISPR- and transposon-associated molecular machineries, including a co-complex between the DNA-targeting complex Cascade and the transposition protein TniQ. Integration of donor DNA occurs in one of two possible orientations at a fixed distance downstream of target DNA sequences, and can accommodate variable length genetic payloads. Deep-sequencing experiments reveal highly specific, genome-wide DNA insertion across dozens of unique target sites. This discovery of a fully programmable, RNA-guided integrase lays the foundation for genomic manipulations that obviate the requirements for double-strand breaks and homology-directed repair.

RNA-guided DNA insertion with CRISPR-associated transposases

Abstract

CRISPR-Cas nucleases are powerful tools for manipulating nucleic acids; however, targeted insertion of DNA remains a challenge, as it requires host cell repair machinery. Here we characterize a CRISPR-associated transposase from cyanobacteria *Scytonema hofmanni* (ShCAST) that consists of Tn7-like transposase subunits and the type V-K CRISPR effector (Cas12k). ShCAST catalyzes RNA-guided DNA transposition by unidirectionally inserting segments of DNA 60 to 66 base pairs downstream of the protospacer. ShCAST integrates DNA into targeted sites in the *Escherichia coli* genome with frequencies of up to 80% without positive selection. This work expands our understanding of the functional diversity of CRISPR-Cas systems and establishes a paradigm for precision DNA insertion.

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A genetically encoded probe for imaging nascent and mature HA-tagged proteins in vivo

Ning Zhao, Kouta Kamijo, Philip D. Fox, Haruka Oda, Tatsuya Morisaki, Yuko Sato, Hiroshi Kimura & Timothy J. Stasevich

Nature Communications **10**, Article number: 2947 (2019) | Download Citation

Abstract

To expand the toolbox of imaging in living cells, we have engineered a single-chain variable fragment binding the linear HA epitope with high affinity and specificity in vivo. The resulting probe, called the HA frankenbody, can light up in multiple colors HA-tagged nuclear, cytoplasmic, membrane, and mitochondrial proteins in diverse cell types. The HA frankenbody also enables state-of-the-art single-molecule experiments in living cells, which we demonstrate by tracking single HA-tagged histones in U2OS cells and single mRNA translation dynamics in both U2OS cells and neurons. Together with the SunTag, we also track two mRNA species simultaneously to demonstrate comparative single-molecule studies of translation can now be done with genetically encoded tools alone. Finally, we use the HA frankenbody to precisely quantify the expression of HA-tagged proteins in developing zebrafish embryos. The versatility of the HA frankenbody makes it a powerful tool for imaging protein dynamics in vivo.

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Multi-Color Single-Molecule Imaging Uncovers Extensive Heterogeneity in mRNA Decoding

mRNA translation is a key step in decoding genetic information. Genetic decoding is surprisingly heterogeneous because multiple distinct polypeptides can be synthesized from a single mRNA sequence. To study translational heterogeneity, we developed the MoonTag, a fluorescence labeling system to visualize translation of single mRNAs. When combined with the orthogonal SunTag system, the MoonTag enables dual readouts of translation, greatly expanding the possibilities to interrogate complex translational heterogeneity. By placing MoonTag and SunTag sequences in different translation reading frames, each driven by distinct translation start sites, start site selection of individual ribosomes can be visualized in real time. We find that start site selection is largely stochastic but that the probability of using a particular start site differs among mRNA molecules and can be dynamically regulated over time. This study provides key insights into translation start site selection heterogeneity and provides a powerful toolbox to visualize complex translation dynamics.

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The Translational Landscape of the Human Heart

Gene expression in human tissue has primarily been studied on the transcriptional level, largely neglecting translational regulation. Here, we analyze the translatomes of 80 human hearts to identify new translation events and quantify the effect of translational regulation. We show extensive translational control of cardiac gene expression, which is orchestrated in a process-specific manner. Translation downstream of predicted disease-causing protein-truncating variants appears to be frequent, suggesting inefficient translation termination. We identify hundreds of previously undetected microproteins, expressed from lncRNAs and circRNAs, for which we validate the protein products *in vivo*. The translation of microproteins is not restricted to the heart and prominent in the translatomes of human kidney and liver. We associate these microproteins with diverse cellular processes and compartments and find that many locate to the mitochondria. Importantly, dozens of microproteins are translated from lncRNAs with well-characterized noncoding functions, indicating previously unrecognized biology.