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Scientific News
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Sven Bulterijs

Business/Conferences/ General news

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HLN+ EXCLUSIEF VOOR ABONNEES

"De kinderen die 135 jaar worden, zijn al geboren", zegt Vlaamse verouderingsexpert

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We willen het niet, maar we verouderen we sowieso: vanaf wanneer beginnen welke onderdelen te verslijten?

Gisteren om 06:00 door Tekst: Chris Snick Illustratie: Lander Ceuppens

Of we het nu willen of niet, verouderen doen we sowieso. Maar vanaf wanneer beginnen onze onderdelen dan te verslijten? Hoewel elke mens anders is, zijn er wel degelijk lijnen in te trekken.

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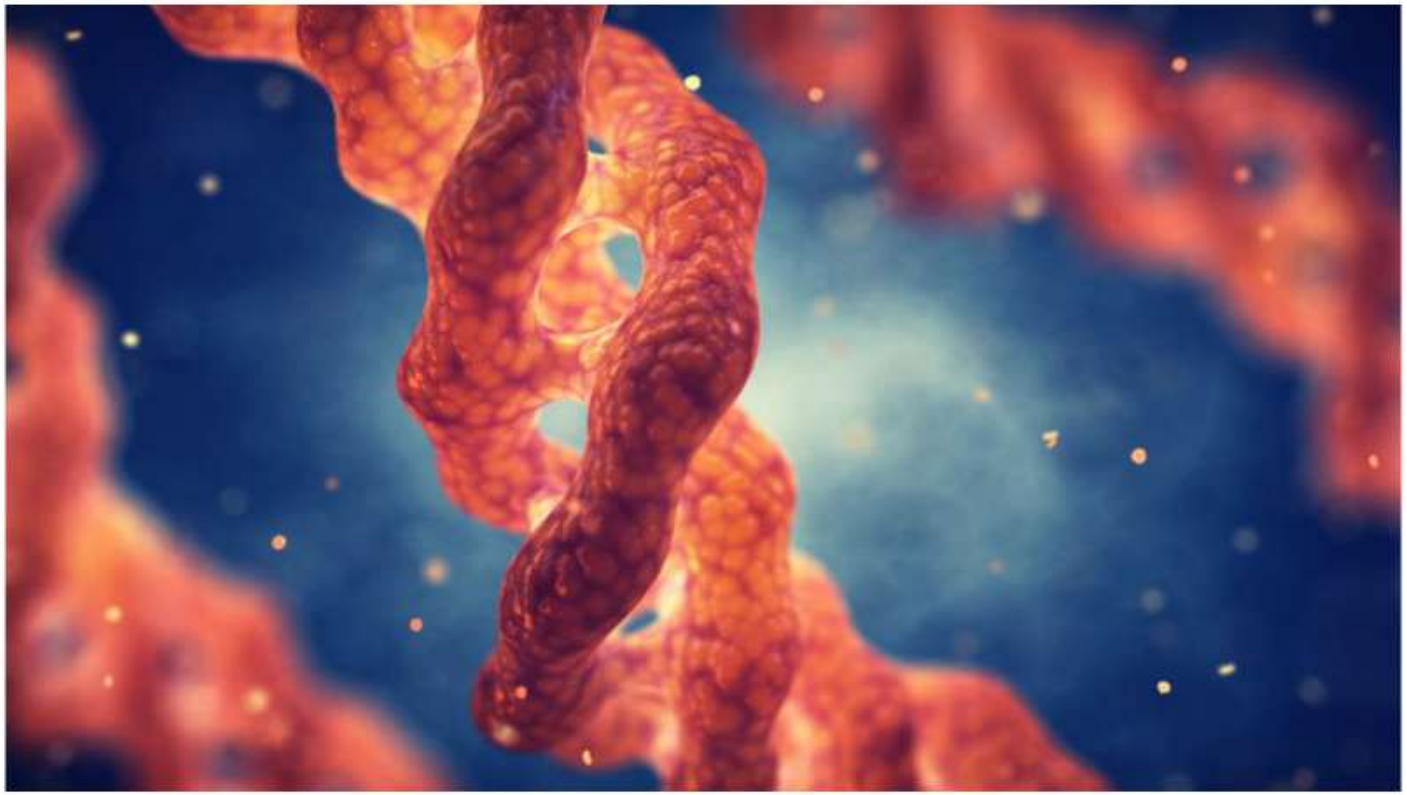
Revel Pharma to Develop Glucosepane Breakers

Steve Hill January 8, 2020 1



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Some pleasant news has recently arrived: Revel Pharmaceuticals has successfully completed a seed round in order to begin developing therapeutics that target glucosepane crosslinks, which are a proposed reason why we age, develop diseases such as diabetes, and suffer from stiffened arteries and hypertension.

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Pfizer teams up with Insilico to mine data for drug targets

by Nick Paul Taylor | Jan 16, 2020 8:59am

Insilico previously teamed up with GlaxoSmithKline to discover new targets and molecules. (Tracy Staton)

Pfizer has **entered** into a research collaboration with Insilico Medicine. The partners will use Insilico's technology to identify real-world evidence for drug targets in multiple therapeutic areas.

Conferences in 2020

Eurosymposium on Healthy Ageing

October 1-3, 2020
Brussels, Belgium

Metabolism, Aging, Pathogenesis, and Stress in *C. elegans*

July 16 - 19, 2020
University of Wisconsin-Madison

-2020-

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Meeting "Metabolism, Aging, Pathogenesis, and Stress" (MAPS 2020), on campus at the son, Memorial Union will host researchers studying fundamental questions regarding ducing aging-associated decline.

Save the Date!

Registration Open: January 23rd
Early Bird Deadline: March 23rd
Oral Abstract Deadline: May 7th
Poster Abstract Deadline: June 4th
Housing Deadline: June 16th

Welcome to the webpage of the 2020 Spring Meeting/3rd Cologne Aging Conference – From Mechanisms to Disease, which will be hosted by the University of Cologne, Germany, on March 18-20, 2020. This biannial meeting has developed into the leading Cologne conference series on the Biology of Aging. For the 2020 conference, we are happy to be hosting internationally leading scientists who will cover various topics of aging research, including:

- mechanisms of epigenetics and DNA damage
- tissue regeneration and senescence
- metabolism and mitochondrial biology
- proteostasis and neuronal aging

Aging research articles

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Codon optimization is an essential parameter for the efficient allotopic expression of mtDNA genes ☆

Mutations in mitochondrial DNA can be inherited or occur *de novo* leading to several debilitating myopathies with no curative option and few or no effective treatments. Allotopic expression of recoded mitochondrial genes from the nucleus has potential as a gene therapy strategy for such conditions, however progress in this field has been hampered by technical challenges. Here we employed codon optimization as a tool to re-engineer the protein-coding genes of the human mitochondrial genome for robust, efficient expression from the nucleus. All 13 codon-optimized constructs exhibited substantially higher protein expression than minimally-recoded genes when expressed transiently, and steady-state mRNA levels for optimized gene constructs were 5–180 fold enriched over recoded versions in stably-selected wildtype cells. Eight of thirteen mitochondria-encoded oxidative phosphorylation (OxPhos) proteins maintained protein expression following stable selection, with mitochondrial localization of expression products. We also assessed the utility of this strategy in rescuing mitochondrial disease cell models and found the rescue capacity of allotopic expression constructs to be gene specific. Allotopic expression of codon optimized ATP8 in disease models could restore protein levels and respiratory function, however, rescue of the pathogenic phenotype for another gene, ND1 was only partially successful. These results imply that though codon-optimization alone is not sufficient for functional allotopic expression of most mitochondrial genes, it is an essential consideration in their design.

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A toolbox for the longitudinal assessment of healthspan in aging mice

The number of people aged over 65 is expected to double in the next 30 years. For many, living longer will mean spending more years with the burdens of chronic diseases such as Alzheimer's disease, cardiovascular disease, and diabetes. Although researchers have made rapid progress in developing geroprotective interventions that target mechanisms of aging and delay or prevent the onset of multiple concurrent age-related diseases, a lack of standardized techniques to assess healthspan in preclinical murine studies has resulted in reduced reproducibility and slow progress. To overcome this, major centers in Europe and the United States skilled in healthspan analysis came together to agree on a toolbox of techniques that can be used to consistently assess the healthspan of mice. Here, we describe the agreed toolbox, which contains protocols for echocardiography, novel object recognition, grip strength, rotarod, glucose tolerance test (GTT) and insulin tolerance test (ITT), body composition, and energy expenditure. The protocols can be performed longitudinally in the same mouse over a period of 4–6 weeks to test how candidate geroprotectors affect cardiac, cognitive, neuromuscular, and metabolic health.

A proteomic atlas of senescence-associated secretomes for aging biomarker development

The senescence-associated secretory phenotype (SASP) has recently emerged as a driver of and promising therapeutic target for multiple age-related conditions, ranging from neurodegeneration to cancer. The complexity of the SASP, typically assessed by a few dozen secreted proteins, has been greatly underestimated, and a small set of factors cannot explain the diverse phenotypes it produces in vivo. Here, we present the "SASP Atlas," a comprehensive proteomic database of soluble proteins and exosomal cargo SASP factors originating from multiple senescence inducers and cell types. Each profile consists of hundreds of largely distinct proteins but also includes a subset of proteins elevated in all SASPs. Our analyses identify several candidate biomarkers of cellular senescence that overlap with aging markers in human plasma, including Growth/differentiation factor 15 (GDF15), stanniocalcin 1 (STC1), and serine protease inhibitors (SERPINs), which significantly correlated with age in plasma from a human cohort, the Baltimore Longitudinal Study of Aging (BLSA). Our findings will facilitate the identification of proteins characteristic of senescence-associated phenotypes and catalog potential senescence biomarkers to assess the burden, originating stimulus, and tissue of origin of senescent cells in vivo.

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Elucidating Proteoform Dynamics Underlying the Senescence Associated Secretory Phenotype

Peter F. Doubleday, Luca Fornelli and Neil L. Kelleher*

Primary diploid cells exit the cell cycle in response to exogenous stress or oncogene activation through a process known as cellular senescence. This cell-autonomous tumor-suppressive mechanism is also a major mechanism operative in organismal aging. To date, temporal aspects of senescence remain understudied. Therefore, we use quantitative proteomics to investigate changes following forced $HRAS^{G12V}$ expression and induction of senescence across 1 week in normal diploid fibroblasts. We demonstrate that global intracellular proteomic changes correlate with the emergence of the senescence-associated secretory phenotype and the switch to robust cell cycle exit. The senescence secretome reinforces cell cycle exit, yet is largely detrimental to tissue homeostasis. Previous studies of secretomes rely on ELISA, bottom-up proteomics or RNA-seq. To date, no study to date has examined the proteoform complexity of secretomes to elucidate isoform-specific, post-translational modifications or regulated cleavage of signal peptides. Therefore, we use a quantitative top-down proteomics approach to define the molecular complexity of secreted proteins <30 kDa. We identify multiple forms of immune regulators with known activities and affinities such as distinct forms of interleukin-8, as well as GROα and HMGA1, and temporally resolve secreted proteoform dynamics. Together, our work demonstrates the complexity of the secretome past individual protein accessions and provides motivation for further proteoform-resolved measurements of the secretome.

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Tissue specificity of senescent cell accumulation during physiologic and accelerated aging of mice

Senescent cells accumulate with age in vertebrates and promote aging largely through their senescence-associated secretory phenotype (SASP). Many types of stress induce senescence, including genotoxic stress. ERCC1-XPF is a DNA repair endonuclease required for multiple DNA repair mechanisms that protect the nuclear genome. Humans or mice with reduced expression of this enzyme age rapidly due to increased levels of spontaneous, genotoxic stress. Here, we asked whether this corresponds to an increased level of senescent cells. $p16^{Ink4a}$ and $p21^{Cip1}$ mRNA were increased ~15-fold in peripheral lymphocytes from 4- to 5-month-old $Ercc1^{-/\Delta}$ and 2.5-year-old wild-type (WT) mice, suggesting that these animals exhibit a similar biological age. $p16^{Ink4a}$ and $p21^{Cip1}$ mRNA were elevated in 10 of 13 tissues analyzed from 4- to 5-month-old $Ercc1^{-/\Delta}$ mice, indicating where endogenous DNA damage drives senescence in vivo. Aged WT mice had similar increases of $p16^{Ink4a}$ and $p21^{Cip1}$ mRNA in the same 10 tissues as the mutant mice. Senescence-associated β–galactosidase activity and $p21^{Cip1}$ protein also were increased in tissues of the progeroid and aged mice, while Lamin B1 mRNA and protein levels were diminished. In $Ercc1^{-/\Delta}$ mice with a $p16^{Ink4a}$ luciferase reporter, bioluminescence rose steadily with age, particularly in lung, thymus, and pancreas. These data illustrate where senescence occurs with natural and accelerated aging in mice and the relative extent of senescence among tissues. Interestingly, senescence was greater in male mice until the end of life. The similarities between $Ercc1^{-/\Delta}$ and aged WT mice support the conclusion that the DNA repair-deficient mice accurately model the age-related accumulation of senescent cells, albeit six-times faster.

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Astrocyte senescence promotes glutamate toxicity in cortical neurons

Chandani Limbad, Tal Ronnen Oron, Fatouma Alimirah, Albert R. Davalos, Tara E. Tracy, Li Gan, Pierre-Yves Desprez, Judith Campisi

Neurodegeneration is a major age-related pathology. Cognitive decline is characteristic of patients with Alzheimer's and related dementias and cancer patients after chemo- or radio-therapies. A recently emerged driver of these and other age-related pathologies is cellular senescence, a cell fate that entails a permanent cell cycle arrest and pro-inflammatory senescence-associated secretory phenotype (SASP). Although there is a link between inflammation and neurodegenerative diseases, there are many open questions regarding how cellular senescence affects neurodegenerative pathologies. Among the various cell types in the brain, astrocytes are the most abundant. Astrocytes have proliferative capacity and are essential for neuron survival. Here, we investigated the phenotype of primary human astrocytes made senescent by X-irradiation, and identified genes encoding glutamate and potassium transporters as specifically downregulated upon senescence. This down regulation led to neuronal cell death in co-culture assays. Unbiased RNA sequencing of transcripts expressed by non-senescent and senescent astrocytes confirmed that glutamate homeostasis pathway declines upon senescence. Our results suggest a key role for cellular senescence, particularly in astrocytes, in excitotoxicity, which may lead to neurodegeneration including Alzheimer's disease and related dementias.

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Reducing Hypothalamic Stem Cell Senescence Protects against Aging-Associated Physiological Decline

Age-dependent loss of hypothalamic neural stem cells (htNSCs) is important for the pathological consequences of aging; however, it is unclear what drives the senescence of htNSCs. Here, we report that a long non-coding RNA, *Hnscr*, is abundantly expressed in the htNSCs of young mice but decreases markedly in middle-aged mice. We show that depletion of *Hnscr* is sufficient to drive the senescence of htNSCs and aging-like phenotypes in mice. Mechanistically, *Hnscr* binds to Y-box protein 1 (YB-1) to prevent its degradation and thus the attenuation of transcription of the senescence marker gene $p16^{INK4A}$. Through molecular docking, we discovered that a naturally occurring small compound, theaflavin 3-gallate, can mimic the activity of *Hnscr*. Treatment of middle-aged mice with theaflavin 3-gallate reduced the senescence of htNSCs while improving aging-associated pathology. These results point to a mediator of the aging process and one that can be pharmacologically targeted to improve aging-related outcomes.

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Cellular senescence contributes to age-dependent changes in circulating extracellular vesicle cargo and function

Extracellular vesicles (EVs) have emerged as important regulators of inter-cellular and inter-organ communication, in part via the transfer of their cargo to recipient cells. Although circulating EVs have been previously studied as biomarkers of aging, how circulating EVs change with age and the underlying mechanisms that contribute to these changes are poorly understood. Here, we demonstrate that aging has a profound effect on the circulating EV pool, as evidenced by changes in concentration, size, and cargo. Aging also alters particle function; treatment of cells with EV fractions isolated from old plasma reduces macrophage responses to lipopolysaccharide, increases phagocytosis, and reduces endothelial cell responses to vascular endothelial growth factor compared to cells treated with young EV fractions. Depletion studies indicate that $CD63^+$ particles mediate these effects. Treatment of macrophages with EV-like particles revealed that old particles increased the expression of EV miRNAs in recipient cells. Transfection of cells with microRNA mimics recapitulated some of the effects seen with old EV-like particles. Investigation into the underlying mechanisms using bone marrow transplant studies revealed circulating cell age does not substantially affect the expression of aging-associated circulating EV miRNAs in old mice. Instead, we show that cellular senescence contributes to changes in particle cargo and function. Notably, senolytic treatment of old mice shifted plasma particle cargo and function toward that of a younger phenotype. Collectively, these results demonstrate that senescent cells contribute to changes in plasma EVs with age and suggest a new mechanism by which senescent cells can affect cellular functions throughout the body.

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Dasatinib plus quercetin prevents uterine age-related dysfunction and fibrosis in mice.

Cavalcante MB, et al. Aging (Albany NY). 2020.
Show full citation

Abstract

The uterine fibrosis contributes to gestational outcomes. Collagen deposition in the uterus is related to uterine aging. Senolytic therapies are an option for reducing health complications related to aging. We investigated effects of aging and the senolytic drug combination of dasatinib plus quercetin (D+Q) on uterine fibrosis. Forty mice, 20 young females (03-months) and 20 old females (18-months), were analyzed. Young (Y) and old (O) animals were divided into groups of 10 mice, with one treatment (T) group (YT and OT) and another control © group (YC and OC). Comparative analysis of Pi3k/Akt1/mTor and p53 gene expression and related microRNAs (miR34a, miR34b, miR34c, miR146a, miR449a, miR21a, miR126a, and miR181b) among groups was performed to test effects of age and treatment on collagen deposition pathways. Aging promoted downregulation of the Pi3k/Akt1/mTor signaling pathway (P = 0.005, P = 0.031, and P = 0.028, respectively) as well as a reduction in expression of miR34c (P = 0.029), miR126a (P = 0.009), and miR181b (P = 0.007). D+Q treatment increased p53 gene expression (P = 0.041) and decreased miR34a (P = 0.016). Our results demonstrate a role for the Pi3k/Akt1/mTor signaling pathway in uterine aging and suggest for the first time a possible anti-fibrotic effect in the uterus of D+Q senolytic therapy.

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Transplanting cells from old but not young donors causes physical dysfunction in older recipients

Adipose-derived mesenchymal stem cell (ADSC)-based regenerative therapies have shown potential for use in many chronic diseases. Aging diminishes stem cell regenerative potential, yet it is unknown whether stem cells from aged donors cause adverse effects in recipients. ADSCs can be obtained using minimally invasive approaches and possess low immunogenicity. Nevertheless, we found that transplanting ADSCs from old donors, but not those from young donors, induces physical dysfunction in older recipient mice. Using single-cell transcriptomic analysis, we identified a naturally occurring senescent cell-like population in ADSCs primarily from old donors that resembles in vitro-generated senescent cells with regard to a number of key pathways. Our study reveals a previously unrecognized health concern due to ADSCs from old donors and lays the foundation for a new avenue of research to devise interventions to reduce harmful effects of ADSCs from old donors.

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Cysteine Toxicity Drives Age-Related Mitochondrial Decline by Altering Iron Homeostasis

Mitochondria and lysosomes are functionally linked, and their interdependent decline is a hallmark of aging and disease. Despite the long-standing connection between these organelles, the function(s) of lysosomes required to sustain mitochondrial health remains unclear. Here, working in yeast, we show that the lysosome-like vacuole maintains mitochondrial respiration by spatially compartmentalizing amino acids. Defects in vacuole function result in a breakdown in intracellular amino acid homeostasis, which drives age-related mitochondrial decline. Among amino acids, we find that cysteine is most toxic for mitochondria and show that elevated non-vacuolar cysteine impairs mitochondrial respiration by limiting intracellular iron availability through an oxidant-based mechanism. Cysteine depletion or iron supplementation restores mitochondrial health in vacuole-impaired cells and prevents mitochondrial decline during aging. These results demonstrate that cysteine toxicity is a major driver of age-related mitochondrial deterioration and identify vacuolar amino acid compartmentation as a cellular strategy to minimize amino acid toxicity.

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Foot web pentosidine does not covary strongly with age in four species of wild seabirds.

Aleksieva AA, et al. Exp Gerontol. 2020.
Show full citation

Abstract

Age is an important parameter for a variety of ecological applications, including population viability analyses, contaminants monitoring and targeting of individuals for conservation. While many organisms can be aged by annual rings, dentition and other techniques (i.e., fish otoliths, clam growth rings, mammal tooth wear), there are no minimally invasive biomarkers for accurately aging birds in the wild. For the past century, banding has been the only way to identify a bird of known age, which requires continuous effort on a large scale with possibly low return rates. Recent studies have identified pentosidine as a potential biomarker of chronological aging in several bird species. To test this idea in four species of long-lived seabirds, we collected skin biopsies from the foot webs of previously banded, known-age seabirds: black-legged kittiwakes (Rissa tridactyla; 0-19 y old), Atlantic puffins (Fratercula arctica; 5-26 y old), razorbills (Alca torda; 0-15 d old) and thick-billed murres (Uria lomvia; 0-35 y old). Foot web samples were specifically chosen because this was the least invasive site for substantial skin biopsy. Samples were analysed with high performance liquid chromatography to quantify pentosidine levels. Collagen levels were estimated through hydroxyproline assays to normalize pentosidine content across individuals. Kittiwakes displayed a weak correlation ($r^2 = 0.20$) between age and pentosidine/collagen. Puffins (adults only, $r^2 = 0.02$), razorbills (chicks only, $r^2 = 0.08$), and murres (adults, $r^2 = 0.04$) did not show any associations with age. We concluded that pentosidine content in the foot web does not appear to be a reliable method for aging seabirds in the wild. An absence of change in pentosidine in the foot web with age is further evidence that long-lived seabirds may maintain physiological performance into old age.

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Synthesis of an Alkynyl Methylglyoxal Probe to Investigate Nonenzymatic Histone Glycation

Qingfei Zheng, Igor Maksimovic, Akhil Upad, David Guber and Yael David*

Methylglyoxal (MGO) is a reactive dicarbonyl metabolite that modifies histones *in vivo* and induces changes in chromatin structure and function. Here we report the synthesis and application of a chemical probe for investigating MGO-glycation. A two-step synthesis of a Cu-click compatible alkynyl oxoaldehyde probe (AlkMGO) via sequential Dess–Martin and Riley oxidations is presented. This synthesis elevates the accessibility and utility of an important tool for tracking, enriching, and studying MGO-glycation to aid in understanding its underlying biochemical functions.

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Negligible senescence in naked mole rats may be a consequence of well-maintained splicing regulation

Naked mole-rats (NMRs) have amongst the longest lifespans relative to body size of any known, non-volant mammalian species. They also display an enhanced stress resistance phenotype, negligible senescence and very rarely are they burdened with chronic age-related diseases. Alternative splicing (AS) dysregulation is emerging as a potential driver of senescence and ageing. We hypothesised that the expression of splicing factors, important regulators of patterns of AS, may differ in NMRs when compared to other species with relatively shorter lifespans. We designed assays specific to NMR splicing regulatory factors and also to a panel of pre-selected brain-expressed genes known to demonstrate senescence-related alterations in AS in other species, and measured age-related changes in the transcript expression levels of these using embryonic and neonatal developmental stages through to extreme old age in NMR brain samples. We also compared splicing factor expression in both young mouse and NMR spleen and brain samples. Both NMR tissues showed approximately double the expression levels observed in tissues from similarly sized mice. Furthermore, contrary to observations in other species, following a brief period of labile expression in early life stages, adult NMR splicing factors and patterns of AS for functionally relevant brain genes remained remarkably stable for at least two decades. These findings are consistent with a model whereby the conservation of splicing regulation and stable patterns of AS may contribute to better molecular stress responses and the avoidance of senescence in NMRs, contributing to their exceptional lifespan and prolonged healthspan.

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The somatic mutation landscape of the human body

Pablo E. García-Nieto, Ashby J. Morrison & Hunter B. Fraser ✉

Background

Somatic mutations in healthy tissues contribute to aging, neurodegeneration, and cancer initiation, yet they remain largely uncharacterized.

Results

To gain a better understanding of the genome-wide distribution and functional impact of somatic mutations, we leverage the genomic information contained in the transcriptome to uniformly call somatic mutations from over 7500 tissue samples, representing 36 distinct tissues. This catalog, containing over 280,000 mutations, reveals a wide diversity of tissue-specific mutation profiles associated with gene expression levels and chromatin states. For example, lung samples with low expression of the mismatch-repair gene *MLH1* show a mutation signature of deficient mismatch repair. In addition, we find pervasive negative selection acting on missense and nonsense mutations, except for mutations previously observed in cancer samples, which are under positive selection and are highly enriched in many healthy tissues.

Conclusions

These findings reveal fundamental patterns of tissue-specific somatic evolution and shed light on aging and the earliest stages of tumorigenesis.

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Supraphysiological protection from replication stress does not extend mammalian lifespan

Replication Stress (RS) is a type of DNA damage generated at the replication fork, characterized by single-stranded DNA (ssDNA) accumulation, and which can be caused by a variety of factors. Previous studies have reported elevated RS levels in aged cells. In addition, mouse models with a deficient RS response show accelerated aging. However, the relevance of endogenous or physiological RS, compared to other sources of genomic instability, for the normal onset of aging is unknown. We have performed long term survival studies of transgenic mice with extra copies of the *Chk1* and/or *Rrm2* genes, which we previously showed extend the lifespan of a progeroid ATR-hypomorphic model suffering from high levels of RS. In contrast to their effect in the context of progeria, the lifespan of *Chk1*, *Rrm2* and *Chk1/Rrm2* transgenic mice was similar to WT littermates in physiological settings. Most mice studied died due to tumors -mainly lymphomas-irrespective of their genetic background. Interestingly, a slightly higher percentage of transgenic mice developed tumors compared to WT mice. Our results indicate that supraphysiological protection from RS does not extend lifespan, indicating that RS may not be a relevant source of genomic instability on the onset of "normal" aging.

Impaired Myofibroblast Dedifferentiation Contributes to Non-Resolving Fibrosis in Aging.

Kato K, et al. Am J Respir Cell Mol Biol. 2020.
Show full citation

Abstract

Idiopathic pulmonary fibrosis (IPF) is a fatal age-associated disease with no cure. Although IPF is widely regarded as a disease of aging, the cellular mechanisms that contribute to this age-associated predilection remain elusive. In this study, we sought to evaluate the consequences of senescence on myofibroblast cell fate and fibrotic responses to lung injury, in the context of aging. We demonstrate that non-senescent lung myofibroblasts maintain the capacity for dedifferentiation, whereas senescent/IPF myofibroblasts exhibited an impaired capacity for dedifferentiation. We have previously demonstrated that the transcription factor, MyoD, acts as a critical switch in the differentiation and dedifferentiation of myofibroblasts. Here we demonstrate that decreased levels of MyoD preceded myofibroblast dedifferentiation and apoptosis susceptibility in non-senescent cells, whereas MyoD expression remained elevated in senescent/IPF myofibroblasts which failed to undergo dedifferentiation and demonstrated resistance to apoptosis. Genetic strategies to silence MyoD restored susceptibility of IPF myofibroblasts to undergo apoptosis, and led to a partial reversal of age-associated persistent fibrosis in vivo. The capacity for myofibroblast dedifferentiation and subsequent apoptosis may be critical to normal physiologic responses to tissue injury, whereas restricted dedifferentiation and apoptosis-resistance in senescent cells may underlie the progressive nature of age-associated human fibrotic disorders. These studies support the concept that senescence may promote pro-fibrotic effects via impaired myofibroblast dedifferentiation and apoptosis-resistance, which contributes to myofibroblast accumulation and ultimately persistent fibrosis in aging.

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Cross-linking modifications of HDL apoproteins by oxidized phospholipids: Structural characterization, *in vivo* detection, and functional implications

Apolipoprotein A-I (apoA-I) is cross-linked and dysfunctional in human atheroma. Although multiple mechanisms of apoA-I cross-linking have been demonstrated in vitro, the in vivo mechanisms of cross-linking are not well established. We have recently demonstrated the highly selective and efficient modification of high-density lipoprotein (HDL) apoproteins by endogenous oxidized phospholipids (oxPLs), including γ-oxoalkenal phospholipids. In the current study, we report that γ-oxoalkenal phospholipids effectively cross-link apoproteins in HDL. We further demonstrate that cross-linking impairs the cholesterol efflux mediated by apoA-I or HDL3 in vitro and in vivo. Using LC–MS/MS analysis, we analyzed the pattern of apoprotein cross-linking in isolated human HDL either by synthetic γ-oxoalkenal phospholipids or by oxPLs generated during HDL oxidation in plasma by the physiologically relevant MPO–H_2O_2–NO_2^- system. We found that five histidine residues in helices 5–8 of apoA-I are preferably cross-linked by oxPLs, forming stable pyrrole adducts with lysine residues in the helices 3–4 of another apoA-I or in the central domain of apoA-II. We also identified cross-links of apoA-I and apoA-II with two minor HDL apoproteins, apoA-IV and apoE. We detected a similar pattern of apoprotein cross-linking in oxidized murine HDL. We further detected oxPL cross-link adducts of HDL apoproteins in plasma and aorta of hyperlipidemic $LDLR^{-/-}$ mice, including cross-link adducts of apoA-I His-165–apoA-I Lys-93, apoA-I His-154–apoA-I Lys-105, apoA-I His-154–apoA-IV Lys-149, and apoA-II Lys-30–apoE His-227. These findings suggest an important mechanism that contributes to the loss of HDL's atheroprotective function in vivo.

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Macrophage Metabolism of Apoptotic Cell-Derived Arginine Promotes Continual Efferocytosis and Resolution of Injury

Continual efferocytic clearance of apoptotic cells (ACs) by macrophages prevents necrosis and promotes injury resolution. How continual efferocytosis is promoted is not clear. Here, we show that the process is optimized by linking the metabolism of engulfed cargo from initial efferocytic events to subsequent rounds. We found that continual efferocytosis is enhanced by the metabolism of AC-derived arginine and ornithine to putrescine by macrophage arginase 1 (Arg1) and ornithine decarboxylase (ODC). Putrescine augments HuR-mediated stabilization of the mRNA encoding the GTP-exchange factor Dbl, which activates actin-regulating Rac1 to facilitate subsequent rounds of AC internalization. Inhibition of any step along this pathway after first-AC uptake suppresses second-AC internalization, whereas putrescine addition rescues this defect. Mice lacking myeloid Arg1 or ODC have defects in efferocytosis *in vivo* and in atherosclerosis regression, while treatment with putrescine promotes atherosclerosis resolution. Thus, macrophage metabolism of AC-derived metabolites allows for optimal continual efferocytosis and resolution of injury.

Dipeptidyl peptidase-4 is increased in the abdominal aortic aneurysm vessel wall and is associated with aneurysm disease processes

Background

Abdominal aortic aneurysm (AAA) is a potentially life-threatening disease, and until today there is no other treatment available than surgical intervention. Dipeptidyl peptidase-4 (DPP4)-inhibitors, used clinically to treat type 2 diabetes, have in murine models been shown to attenuate aneurysm formation and decrease aortic wall matrix degradation, inflammation and apoptosis. Our aim was to investigate if DPP4 is present, active and differentially expressed in human AAA.

Methods and results

DPP4 gene expression was elevated in both media and adventitia of AAA tissue compared with control tissue, as measured by microarrays and qPCR, with consistent findings in external data. The plasma activity of DPP4 was however lower in male patients with AAA compared with age- and gender-matched controls, independently of comorbidity or medication. Immunohistochemical double staining revealed co-localization of DPP4 with cells positive for CD68, CD4 and -8, CD20, and SMA. Gene set enrichment analysis demonstrated that expression of DPP4 in AAA tissue correlated with expression of biological processes related to B- and T-cells, extracellular matrix turnover, peptidase activity, oxidative stress and angiogenesis whereas it correlated negatively with muscle-/actin-related processes.

Conclusion

DPP4 is upregulated in both media and adventitia of human AAA and correlates with aneurysm pathophysiological processes. These results support previous murine mechanistic studies and implicate DPP4 as a target in AAA disease.

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Behav Brain Res. 2020 Jan 22:112502. doi: 10.1016/j.bbr.2020.112502. [Epub ahead of print]

Is there a relationship between low-grade systemic inflammation and cognition in healthy people aged 60-75 years?

Fard MT[1], Cribb L[2], Nolidin K[1], Savage K[1], Wesnes K[3], Stough C[4].

Author information

Abstract

Although inflammation has been associated with cognitive impairment in dementia, less is known about its role in the cognition of middle to older aged healthy people. This study utilised baseline data from the Australian Research Council Longevity Intervention (ARCLI) trial to investigate the relationship between markers of systemic inflammation (TNF-α, IL-6, IL-1β, INF-γ, IL-2, IL-4, IL-10 and hsCRP) and cognitive function in 286 healthy volunteers aged 60-75 years. We assessed cognitive functioning across domains including attention, speed of memory, working memory and episodic memory using the Cognitive Drug Research test battery. Only IFN-γ was related to cognitive function, being associated with greater odds of having low continuity of attention (log2 IFN-γ OR, 1.46; 95% CI, 1.18-1.85). The relationship between episodic memory, speed of memory and inflammation varied with BMI. In high BMI participants, increased inflammation was associated with worse cognitive function, while this association was reversed in those with low BMI. Outside of the influence of IFN-γ on attention, low-grade systemic inflammation was not robustly associated with cognitive function in this sample of middle to older aged healthy people. Further research is required to understand the role of BMI in the intersection of inflammation and cognitive function.

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Clonally expanded CD8 T cells patrol the cerebrospinal fluid in Alzheimer's disease

Alzheimer's disease is an incurable neurodegenerative disorder in which neuroinflammation has a critical function[1]. However, little is known about the contribution of the adaptive immune response in Alzheimer's disease[2]. Here, using integrated analyses of multiple cohorts, we identify peripheral and central adaptive immune changes in Alzheimer's disease. First, we performed mass cytometry of peripheral blood mononuclear cells and discovered an immune signature of Alzheimer's disease that consists of increased numbers of $CD8^+$ T effector memory $CD45RA^+$ (T_{EMRA}) cells. In a second cohort, we found that $CD8^+$ T_{EMRA} cells were negatively associated with cognition. Furthermore, single-cell RNA sequencing revealed that T cell receptor (TCR) signalling was enhanced in these cells. Notably, by using several strategies of single-cell TCR sequencing in a third cohort, we discovered clonally expanded $CD8^+$ T_{EMRA} cells in the cerebrospinal fluid of patients with Alzheimer's disease. Finally, we used machine learning, cloning and peptide screens to demonstrate the specificity of clonally expanded TCRs in the cerebrospinal fluid of patients with Alzheimer's disease to two separate Epstein–Barr virus antigens. These results reveal an adaptive immune response in the blood and cerebrospinal fluid in Alzheimer's disease and provide evidence of clonal, antigen-experienced T cells patrolling the intrathecal space of brains affected by age-related neurodegeneration.

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β-amyloid redirects norepinephrine signaling to activate the pathogenic GSK3β/tau cascade

The brain noradrenergic system is critical for normal cognition and is affected at early stages in Alzheimer's disease (AD). Here, we reveal a previously unappreciated direct role of norepinephrine signaling in connecting β-amyloid (Aβ) and tau, two key pathological components of AD pathogenesis. Our results show that Aβ oligomers bind to an allosteric site on α_{2A} adrenergic receptor (α_{2A}AR) to redirect norepinephrine-elicited signaling to glycogen synthase kinase 3β (GSK3β) activation and tau hyperphosphorylation. This norepinephrine-dependent mechanism sensitizes pathological GSK3β/tau activation in response to nanomolar accumulations of extracellular Aβ, which is 50- to 100-fold lower than the amount required to activate GSK3β by Aβ alone. The significance of our findings is supported by in vivo evidence in two mouse models, human tissue sample analysis, and longitudinal clinical data. Our study provides translational insights into mechanisms underlying Aβ proteotoxicity, which might have strong implications for the interpretation of Aβ clearance trial results and future drug design and for understanding the selective vulnerability of noradrenergic neurons in AD.

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Prospective longitudinal atrophy in Alzheimer's disease correlates with the intensity and topography of baseline tau-PET

β-Amyloid plaques and tau-containing neurofibrillary tangles are the two neuropathological hallmarks of Alzheimer's disease (AD) and are thought to play crucial roles in a neurodegenerative cascade leading to dementia. Both lesions can now be visualized in vivo using positron emission tomography (PET) radiotracers, opening new opportunities to study disease mechanisms and improve patients' diagnostic and prognostic evaluation. In a group of 32 patients at early symptomatic AD stages, we tested whether β-amyloid and tau-PET could predict subsequent brain atrophy measured using longitudinal magnetic resonance imaging acquired at the time of PET and 15 months later. Quantitative analyses showed that the global intensity of tau-PET, but not β-amyloid–PET, signal predicted the rate of subsequent atrophy, independent of baseline cortical thickness. Additional investigations demonstrated that the specific distribution of tau-PET signal was a strong indicator of the topography of future atrophy at the single patient level and that the relationship between baseline tau-PET and subsequent atrophy was particularly strong in younger patients. These data support disease models in which tau pathology is a major driver of local neurodegeneration and highlight the relevance of tau-PET as a precision medicine tool to help predict individual patient's progression and design future clinical trials.

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Mild behavioral impairment is associated with β-amyloid but not tau or neurodegeneration in cognitively intact elderly individuals.

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⊕ Author information

Abstract

INTRODUCTION: Mild behavioral impairment (MBI) is characterized by the emergence of neuropsychiatric symptoms in elderly persons. Here, we examine the associations between MBI and Alzheimer's disease (AD) biomarkers in asymptomatic elderly individuals.

METHODS: Ninety-six cognitively normal elderly individuals underwent MRI, [^{18}F]AZD4694 β-amyloid-PET, and [^{18}F]MK6240 tau-PET. MBI was assessed using the MBI Checklist (MBI-C). Pearson's correlations and voxel-based regressions were used to evaluate the relationship between MBI-C score and [^{18}F]AZD4694 retention, [^{18}F]MK6240 retention, and gray matter (GM) volume.

RESULTS: Pearson correlations revealed a positive relationship between MBI-C score and global and striatal [^{18}F]AZD4694 standardized uptake value ratios (SUVRs). Voxel-based regression analyses revealed a positive correlation between MBI-C score and [^{18}F]AZD4694 retention. No significant correlations were found between MBI-C score and [^{18}F]MK6240 retention or GM volume.

CONCLUSION: We demonstrate for the first time a link between MBI and early AD pathology in a cognitively intact elderly population, supporting the use of the MBI-C as a metric to enhance clinical trial enrolment.

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HEALTHY LIFE EXTENSION SOCIETY

Alzheimer's Disease Neuropathological Comorbidities Are Common in the Younger-Old

Clinicopathological studies have demonstrated that Alzheimer's disease dementia (ADD) is often accompanied by clinically undetectable comorbid neurodegenerative and cerebrovascular disease that alter the presence and rate of cognitive decline in aging and ADD. Aside from causing increased variability in clinical response, it is possible that the major ADD comorbidities may not respond to ADD-specific molecular therapeutics. As most reports have focused on comorbidity in the oldest-old, its extent in younger age groups that are more likely to be involved in clinical trials is largely unknown. We conducted a survey of neuropathological comorbidities in sporadic ADD using data from the US National Alzheimer's Coordinating Center. Subject data was restricted to those with dementia and meeting National Institute on Aging-Alzheimer's Association (NIA-AA) intermediate or high AD Neuropathological Change (ADNC) levels, excluding those with known autosomal dominant AD-related mutations. Subjects were divided into age-at-death categories for analysis: under 60, 60-69, 70-79, 80-89, 90-99 and 100 or over. Confirmatory of earlier reports, ADD histopathology is less severe with advancing age, effectively increasing the relative contribution of comorbidities, most of which rise in prevalence with age. Highly prevalent ADD comorbidities are not restricted to the oldest-old but are common even in early-onset ADD. The percentage of cases with ADD as the sole major neuropathological diagnosis is highest in the under-60 group, where "pure" ADD cases are still in the minority at 44%. After this AD as a sole major pathology in ADD declines to roughly 20% in the 70s and beyond. Comorbidity rates for some pathologies, especially LBD, are high even in subjects in their 60s and 70s, at nearly 60%, but for most others, their prevalence increases with age. TDP-43 pathology affects more than 35% of ADD subjects 80 and over while microscopic infarcts reach this rate a decade later. Gross infarcts rise more slowly and affect fewer subjects but still involve 15-20% of ADD after age 80. White matter rarefaction may be underestimated in the NACC database but is present in almost 70% of centenarians with ADD. Effective clinical trials depend on accurate estimates of required subject numbers, which are dependent on observed effect size and clinical response variability. Comorbidities are likely to affect both, leading to lower probability of clinical trial success. Stratifying ADD clinical trial analyses by presence and types of accompanying comorbidities might identify subgroups with higher effect sizes and greater clinical response rates, but accurate in-vivo diagnostic methods for most comorbidities are still lacking.

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Synthetic Evidence of the Amadori-Type Alkylation of Biogenic Amines by the Neurotoxic Metabolite Dopegal

The neurotransmitter metabolite 3,4-dihydroxy-phenylglycolaldehyde (dopegal) damages neurons and the myocardium by protein cross-linking, resulting in conglomerations and cell death. We investigated this process on a synthetic scale, leading to the discovery of an Amadori-type rearrangement of dopegal in the reaction with several amino acids and neuropeptides. This alkylation also occurs with neurotransmitters, suggesting an influence of dopegal on neurochemical processes. The rearrangement occurs readily under physiological conditions.

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Increasing neurogenesis refines hippocampal activity rejuvenating navigational learning strategies and contextual memory throughout life

Functional plasticity of the brain decreases during ageing causing marked deficits in contextual learning, allocentric navigation and episodic memory. Adult neurogenesis is a prime example of hippocampal plasticity promoting the contextualisation of information and dramatically decreases during ageing. We found that a genetically-driven expansion of neural stem cells by overexpression of the cell cycle regulators Cdk4/cyclinD1 compensated the age-related decline in neurogenesis. This triggered an overall inhibitory effect on the trisynaptic hippocampal circuit resulting in a changed profile of CA1 sharp-wave ripples known to underlie memory consolidation. Most importantly, increased neurogenesis rescued the age-related switch from hippocampal to striatal learning strategies by rescuing allocentric navigation and contextual memory. Our study demonstrates that critical aspects of hippocampal function can be reversed in old age, or compensated throughout life, by exploiting the brain's endogenous reserve of neural stem cells.

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HEALTHY LIFE EXTENSION SOCIETY

The lipid elongation enzyme ELOVL2 is a molecular regulator of aging in the retina

Methylation of the regulatory region of the elongation of very-long-chain fatty acids-like 2 (*ELOVL2*) gene, an enzyme involved in elongation of long-chain polyunsaturated fatty acids, is one of the most robust biomarkers of human age, but the critical question of whether *ELOVL2* plays a functional role in molecular aging has not been resolved. Here, we report that *Elovl2* regulates age-associated functional and anatomical aging in vivo, focusing on mouse retina, with direct relevance to age-related eye diseases. We show that an age-related decrease in *Elovl2* expression is associated with increased DNA methylation of its promoter. Reversal of *Elovl2* promoter hypermethylation in vivo through intravitreal injection of 5-Aza-2'-deoxycytidine (5-Aza-dc) leads to increased *Elovl2* expression and rescue of age-related decline in visual function. Mice carrying a point mutation C234W that disrupts *Elovl2*-specific enzymatic activity show electrophysiological characteristics of premature visual decline, as well as early appearance of autofluorescent deposits, well-established markers of aging in the mouse retina. Finally, we find deposits underneath the retinal pigment epithelium in *Elovl2* mutant mice, containing components found in human drusen, a pathologic hallmark of age related macular degeneration. These findings indicate that ELOVL2 activity regulates aging in mouse retina, provide a molecular link between polyunsaturated fatty acids elongation and visual function, and suggest novel therapeutic strategies for the treatment of age-related eye diseases.

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HEALTHY LIFE EXTENSION SOCIETY

Sestrin prevents atrophy of disused and aging muscles by integrating anabolic and catabolic signals

A unique property of skeletal muscle is its ability to adapt its mass to changes in activity. Inactivity, as in disuse or aging, causes atrophy, the loss of muscle mass and strength, leading to physical incapacity and poor quality of life. Here, through a combination of transcriptomics and transgenesis, we identify sestrins, a family of stress-inducible metabolic regulators, as protective factors against muscle wasting. Sestrin expression decreases during inactivity and its genetic deficiency exacerbates muscle wasting; conversely, sestrin overexpression suffices to prevent atrophy. This protection occurs through mTORC1 inhibition, which upregulates autophagy, and AKT activation, which in turn inhibits FoxO-regulated ubiquitin–proteasome-mediated proteolysis. This study reveals sestrin as a central integrator of anabolic and degradative pathways preventing muscle wasting. Since sestrin also protected muscles against aging-induced atrophy, our findings have implications for sarcopenia.

Heales
HEALTHY LIFE EXTENSION SOCIETY

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Molecular and Functional Networks Linked to Sarcopenia Prevention by Caloric Restriction in Rhesus Monkeys.

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⊕ Author information

Abstract

Caloric restriction (CR) improves survival in nonhuman primates and delays the onset of age-related morbidities including sarcopenia, which is characterized by the age-related loss of muscle mass and function. A shift in metabolism anticipates the onset of muscle-aging phenotypes in nonhuman primates, suggesting a potential role for metabolism in the protective effects of CR. Here, we show that CR induced profound changes in muscle composition and the cellular metabolic environment. Bioinformatic analysis linked these adaptations to proteostasis, RNA processing, and lipid synthetic pathways. At the tissue level, CR maintained contractile content and attenuated age-related metabolic shifts among individual fiber types with higher mitochondrial activity, altered redox metabolism, and smaller lipid droplet size. Biometric and metabolic rate data confirm preserved metabolic efficiency in CR animals that correlated with the attenuation of age-related muscle mass and physical activity. These data suggest that CR-induced reprogramming of metabolism plays a role in delayed aging of skeletal muscle in rhesus monkeys.

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HEALTHY LIFE EXTENSION SOCIETY

Deletion of Nrf2 shortens lifespan in C57BL6/J male mice but does not alter the health and survival benefits of caloric restriction

Caloric restriction (CR) is the leading non-pharmaceutical dietary intervention to improve health- and lifespan in most model organisms. A wide array of cellular pathways is induced in response to CR and CR-mimetics, including the transcriptional activator Nuclear factor erythroid-2-related factor 2 (Nrf2), which is essential in the upregulation of multiple stress-responsive and mitochondrial enzymes. Nrf2 is necessary in tumor protection but is not essential for the lifespan extending properties of CR in outbred mice. Here, we sought to study Nrf2-knockout (KO) mice and littermate controls in male C57BL6/J, an inbred mouse strain. Deletion of Nrf2 resulted in shortened lifespan compared to littermate controls only under ad libitum conditions. CR-mediated lifespan extension and physical performance improvements did not require Nrf2. Metabolic and protein homeostasis and activation of tissue-specific cytoprotective proteins were dependent on Nrf2 expression. These results highlight an important contribution of Nrf2 for normal lifespan and stress response.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Identification of a blood test-based biomarker of aging through deep learning of aging trajectories in large phenotypic datasets of mice

Konstantin Avchaciov, Marina P. Antoch, Ekaterina L. Andrianova, Andrei E. Tarkhov, Leonid I. Menshikov, Andrei V. Gudkov, Peter O. Fedichev

We proposed and characterized a novel biomarker of aging and frailty in mice trained from the large set of the most conventional, easily measured blood parameters such as Complete Blood Counts (CBC) from the open-access Mouse Phenome Database (MPD). Instead of postulating the existence of an aging clock associated with any particular subsystem of an aging organism, we assumed that aging arises cooperatively from positive feedback loops spanning across physiological compartments and leading to an organism-level instability of the underlying regulatory network. To analyze the data, we employed a deep artificial neural network including auto-encoder (AE) and auto-regression (AR) components. The AE was used for dimensionality reduction and denoising the data. The AR was used to describe the dynamics of an individual mouse's health state by means of stochastic evolution of a single organism state variable, the "dynamic frailty index" (dFI), that is the linear combination of the latent AE features and has the meaning of the total number of regulatory abnormalities developed up to the point of the measurement or, more formally, the order parameter associated with the instability. We used neither the chronological age nor the remaining lifespan of the animals while training the model. Nevertheless, dFI fully described aging on the organism level, that is it increased exponentially with age and predicted remaining lifespan. Notably, dFI correlated strongly with multiple hallmarks of aging such as physiological frailty index, indications of physical decline, molecular markers of inflammation and accumulation of senescent cells. The dynamic nature of dFI was demonstrated in mice subjected to aging acceleration by placement on a high-fat diet and aging deceleration by treatment with rapamycin.

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HEALTHY LIFE EXTENSION SOCIETY

Personal aging markers and ageotypes revealed by deep longitudinal profiling

The molecular changes that occur with aging are not well understood[1,2,3,4]. Here, we performed longitudinal and deep multiomics profiling of 106 healthy individuals from 29 to 75 years of age and examined how different types of 'omic' measurements, including transcripts, proteins, metabolites, cytokines, microbes and clinical laboratory values, correlate with age. We identified both known and new markers that associated with age, as well as distinct molecular patterns of aging in insulin-resistant as compared to insulin-sensitive individuals. In a longitudinal setting, we identified personal aging markers whose levels changed over a short time frame of 2–3 years. Further, we defined different types of aging patterns in different individuals, termed 'ageotypes', on the basis of the types of molecular pathways that changed over time in a given individual. Ageotypes may provide a molecular assessment of personal aging, reflective of personal lifestyle and medical history, that may ultimately be useful in monitoring and intervening in the aging process.

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Multi-faceted deregulation of gene expression and protein synthesis with age

Protein synthesis represents a major metabolic activity of the cell. However, how it is affected by aging and how this in turn impacts cell function remains largely unexplored. To address this question, herein we characterized age-related changes in both the transcriptome and translatome of mouse tissues over the entire lifespan. Expression of the majority of differentially expressed genes followed a U-shaped curve with the turning point around 3-months-old. We showed that transcriptome changes govern changes in the translatome and are associated with altered expression of genes involved in inflammation, extracellular matrix and lipid metabolism. We also identified genes that may serve as candidate biomarkers of aging. At the translational level, we uncovered sustained down-regulation of a set of 5' terminal oligopyrimidine (5'TOP) transcripts encoding protein synthesis and ribosome biogenesis machinery and regulated by the mTOR pathway. For many of them, ribosome occupancy dropped 3-fold or even more. Moreover, with age, ribosome coverage gradually decreased in the vicinity of start codons and increased near stop codons, revealing complex age-related changes in the translation process. Taken together, our results reveal systematic and multi-dimensional deregulation in protein synthesis, showing how this major cellular process declines with age.

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HEALTHY LIFE EXTENSION SOCIETY

Cell-to-Cell Variation in Gene Expression for Cultured Human Cells Is Controlled in Trans by Diverse Genes: Implications for the Pathobiology of Aging

Cell-to-cell variation in gene expression increases among homologous cells within multiple tissues during aging. We call this phenomenon variegated gene expression (VGE). Long, healthy life requires robust and *coordinated* gene expression. We posit that nature may have evolved VGE as a bet-hedging mechanism to protect reproductively active populations. The price we may pay is accelerated aging. That hypothesis will require the demonstration that genetic loci are capable of modulating degrees of VGE. While loci controlling VGE in yeast and genes controlling interindividual variation in gene expression in *Caenorhabditis elegans* have been identified, there has been no compelling evidence for the role of specific genetic loci in modulations of VGE of specific targets in humans. With the assistance of a core facility, we used a customized library of siRNA constructs to screen 1,195 human genes to identify loci contributing to the control of VGE of a gene with relevance to the biology of aging. We identified approximately 50 loci controlling VGE of the prolongevity gene, *SIRT1*. Because of its partial homology to *FOXO3A*, a variant of which is enriched in centenarians, our laboratory independently confirmed that the knockdown of *FOXF2* greatly diminished VGE of *SIRT1* but had little impact upon the VGE of *WRN*. While the role of these VGE-altering genes on aging in vivo remains to be determined, we hypothesize that some of these genes can be targeted to increase functionality during aging.

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HEALTHY LIFE EXTENSION SOCIETY

Hyperactivation of sympathetic nerves drives depletion of melanocyte stem cells

Empirical and anecdotal evidence has associated stress with accelerated hair greying (formation of unpigmented hairs)[1,2], but so far there has been little scientific validation of this link. Here we report that, in mice, acute stress leads to hair greying through the fast depletion of melanocyte stem cells. Using a combination of adrenalectomy, denervation, chemogenetics[3,4], cell ablation and knockout of the adrenergic receptor specifically in melanocyte stem cells, we find that the stress-induced loss of melanocyte stem cells is independent of immune attack or adrenal stress hormones. Instead, hair greying results from activation of the sympathetic nerves that innervate the melanocyte stem-cell niche. Under conditions of stress, the activation of these sympathetic nerves leads to burst release of the neurotransmitter noradrenaline (also known as norepinephrine). This causes quiescent melanocyte stem cells to proliferate rapidly, and is followed by their differentiation, migration and permanent depletion from the niche. Transient suppression of the proliferation of melanocyte stem cells prevents stress-induced hair greying. Our study demonstrates that neuronal activity that is induced by acute stress can drive a rapid and permanent loss of somatic stem cells, and illustrates an example in which the maintenance of somatic stem cells is directly influenced by the overall physiological state of the organism.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Intermittent fasting from dawn to sunset for 30 consecutive days is associated with anticancer proteomic signature and upregulates key regulatory proteins of glucose and lipid metabolism, circadian clock, DNA repair, cytoskeleton remodeling, immune system and cognitive function in healthy subjects.

Murine studies showed that disruption of circadian clock rhythmicity could lead to cancer and metabolic syndrome. Time-restricted feeding can reset the disrupted clock rhythm, protect against cancer and metabolic syndrome. Based on these observations, we hypothesized that intermittent fasting for several consecutive days without calorie restriction in humans would induce an anticarcinogenic proteome and the key regulatory proteins of glucose and lipid metabolism. Fourteen healthy subjects fasted from dawn to sunset for over 14 h daily. Fasting duration was 30 consecutive days. Serum samples were collected before fasting, at the end of 4th week during 30-day intermittent fasting, and one week after 30-day intermittent fasting. An untargeted serum proteomic profiling was performed using ultra high-performance liquid chromatography/tandem mass spectrometry. Our results showed that 30-day intermittent fasting was associated with an anticancer serum proteomic signature, upregulated key regulatory proteins of glucose and lipid metabolism, circadian clock, DNA repair, cytoskeleton remodeling, immune system, and cognitive function, and resulted in a serum proteome protective against cancer, metabolic syndrome, inflammation, Alzheimer's disease, and several neuropsychiatric disorders. These findings suggest that fasting from dawn to sunset for 30 consecutive days can be preventive and adjunct therapy in cancer, metabolic syndrome, and several cognitive and neuropsychiatric diseases. SIGNIFICANCE: The clinical implications of our study are profound. Our results showed that intermittent fasting from dawn to sunset for over 14 h daily for 30 consecutive days was associated with an anticancer serum proteomic signature and upregulated key regulatory proteins of glucose and lipid metabolism, insulin signaling, circadian clock, DNA repair, cytoskeleton remodeling, immune system, and cognitive function, and resulted in a serum proteome protective against cancer, obesity, diabetes, metabolic syndrome, inflammation, Alzheimer's disease, and several neuropsychiatric disorders. Importantly, these findings occurred in the absence of any calorie restriction and significant weight loss. These findings suggest that intermittent fasting from dawn to sunset can be a preventive and adjunct therapy in cancer, metabolic syndrome and Alzheimer's disease and several neuropsychiatric diseases.

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HEALTHY LIFE EXTENSION SOCIETY

A Molecular Chameleon for Mapping Subcellular Polarity in an Unfolded Proteome Environment

Environmental polarity is an important factor that drives biomolecular interactions to regulate cell function. Herein, a general method of using the fluorogenic probe NTPAN-MI is reported to quantify the subcellular polarity change in response to protein unfolding. NTPAN-MI fluorescence is selectively activated upon labeling unfolded proteins with exposed thiols, thereby reporting on the extent of proteostasis. NTPAN-MI also reveals the collapse of the host proteome caused by influenza A virus infection. The emission profile of NTPAN-MI contains information of the local polarity of the unfolded proteome, which can be resolved through spectral phasor analysis. Under stress conditions that disrupt different checkpoints of protein quality control, distinct patterns of dielectric constant distribution in the cytoplasm can be observed. However, in the nucleus, the unfolded proteome was found to experience a more hydrophilic environment across all the stress conditions, indicating the central role of nucleus in the stress response process.

Heales
HEALTHY LIFE EXTENSION SOCIETY

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The Lifespan Extension Ability of Nicotinic Acid Depends on Whether the Intracellular NAD^+ Level Is Lower than the Sirtuin-Saturating Concentrations.

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Author information

Abstract

Calorie restriction can extend lifespan by increasing intracellular nicotinamide adenine dinucleotide (NAD^+), thereby upregulating the activity of sirtuins (*Caenorhabditis elegans* Sir-2.1; human SIRT1). Nicotinic acid (NA) can be metabolized to NAD^+; however, the calorie restriction mimetic (CRM) potential of NA is unclear. This study explored the ability and mechanism of NA to extend the lifespan of human Hs68 cells and C. elegans. We found that NA can efficiently increase the intracellular NAD^+ levels in Hs68 cells and *C. elegans*; however, NA was only able to extend the lifespan of *C. elegans*. The steady-state NAD^+ level in *C. elegans* was approximately 55 μM. When intracellular NAD^+ was increased by a mutation of pme-1 (poly (ADP-ribose) metabolism enzyme 1) or by pretreatment with NAD^+ in the medium, the lifespan extension ability of NA disappeared. Additionally, the saturating concentration of NAD^+ required by SIRT1 was approximately 200 μM; however, the steady-state concentration of NAD^+ in Hs68 cells reached up to 460 μM. These results demonstrate that the lifespan extension ability of NA depends on whether the intracellular level of NAD^+ is lower than the sirtuin-saturating concentration in Hs68 cells and in *C. elegans*. Thus, the CRM potential of NA should be limited to individuals with lower intracellular NAD^+.

C. elegans aging research

Heales
HEALTHY LIFE EXTENSION SOCIETY

Caenorhabditis Intervention Testing Program: the creatine analog β-guanidinopropionic acid does not extend lifespan in nematodes

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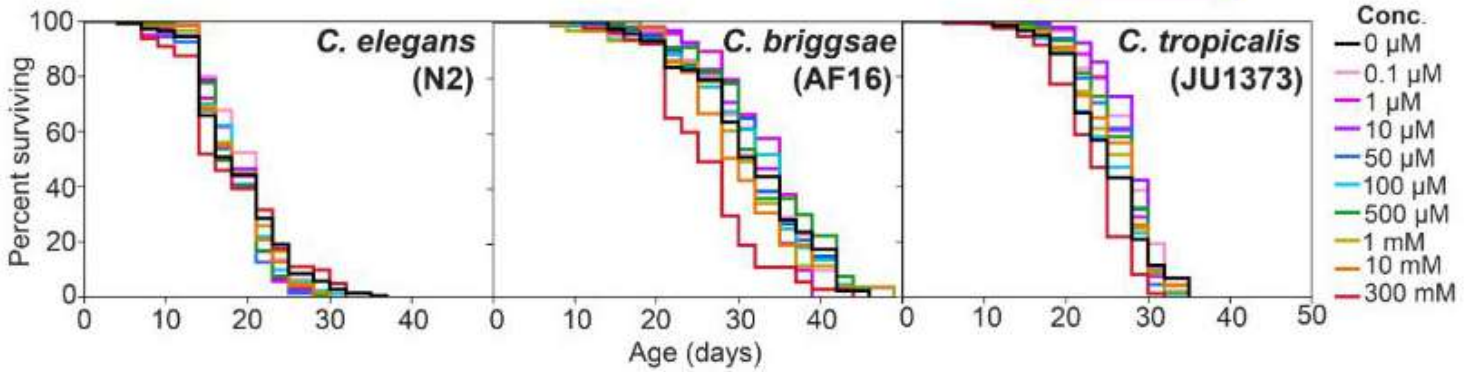
WormBase

PDF

NEGATIVE RESULT

NEW FINDING



Heales
HEALTHY LIFE EXTENSION SOCIETY

Evolutionary causes of lifespan extension by dietary restriction: linking theory and mechanisms

Laura M. Travers, Hanne Carlsson, Elizabeth M. L. Duxbury, Alexei A. Maklakov

Dietary restriction (DR), reduced food intake without malnutrition, increases lifespan across a broad range of taxa, but the evolutionary underpinning of this phenomenon is poorly understood. The resource reallocation hypothesis proposes that dietary restricted animals divert resources from reproduction to somatic maintenance to increase survival in times of nutrient scarcity in favour of future reproduction. The "longevity by-product" hypothesis proposes instead that dietary restricted animals increase nutrient recycling via autophagy to maximise immediate reproduction, thereby reducing cellular toxic waste and leading to longer lifespan as an unselected by-product. The "longevity by-product" hypothesis makes a unique prediction that blocking autophagy in DR animals will simultaneously reduce lifespan and reproduction. To test the adaptive value of autophagy under dietary restriction, we inhibited autophagy using *bec-1* RNAi knockdown in DR and fully-fed *Caenorhabditis elegans* nematodes. Our findings confirm that autophagic inhibition results in a significantly shorter lifespan under DR, suggesting that autophagy is important for survival in times of famine. Remarkably, we also show that inhibiting autophagy throughout adult life significantly increases reproduction in both dietary restricted and fully fed worms. Moreover, this did not come at a transgenerational cost to offspring fitness. Our results suggest that autophagy is an energetically costly process that reduces resources available for reproduction, but is necessary for survival during famine, and are thus consistent with the resource reallocation hypothesis.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Variable environments select for short lifespan

Martin I Lind, Irja I Ratikainen, Johan Andersson, Hanne Carlsson, Therese Krieg, Tuuli Larva, Alexei A Maklakov

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Abstract

The role of environmental variation in the evolution of lifespan is contested. Classic theory suggests that variable environments result in evolution of long life but novel theoretical breakthroughs show that environmental variation can instead select for short lifespan when the changes are rapid relative to generation time. Here we combined simulation modelling and experimental evolution to study the evolution of lifespan in response to temperature variation to provide the first empirical test of the new theory. Genetically diverse populations of the outcrossing nematode Caenorhabditis remanei, were exposed to a novel, stressful temperature for 30 generations, in either stable, slowly increasing or fluctuating temperature regimes. We found evolution of shorter lifespan in populations evolving in rapidly fluctuating environments both in simulation models and in real populations supporting the new theory. While climate warming is predicted to increase environmental stochasticity, our results show that fast temperature cycles rapidly select for short lifespan.

Four glial cells regulate ER stress resistance and longevity via neuropeptide signaling in *C. elegans*

The ability of the nervous system to sense cellular stress and coordinate protein homeostasis is essential for organismal health. Unfortunately, stress responses that mitigate disturbances in proteostasis, such as the unfolded protein response of the endoplasmic reticulum (UPR^{ER}), become defunct with age. In this work, we expressed the constitutively active UPR^{ER} transcription factor, XBP-1s, in a subset of astrocyte-like glia, which extended the life span in *Caenorhabditis elegans*. Glial XBP-1s initiated a robust cell nonautonomous activation of the UPR^{ER} in distal cells and rendered animals more resistant to protein aggregation and chronic ER stress. Mutants deficient in neuropeptide processing and secretion suppressed glial cell nonautonomous induction of the UPR^{ER} and life-span extension. Thus, astrocyte-like glial cells play a role in regulating organismal ER stress resistance and longevity.

Heales
HEALTHY LIFE EXTENSION SOCIETY

DAF-16/FOXO requires Protein Phosphatase 4 to initiate transcription of stress resistance and longevity promoting genes

In *C. elegans*, the conserved transcription factor DAF-16/FOXO is a powerful aging regulator, relaying dire conditions into expression of stress resistance and longevity promoting genes. For some of these functions, including low insulin/IGF signaling (IIS), DAF-16 depends on the protein SMK-1/SMEK, but how SMK-1 exerts this role has remained unknown. We show that SMK-1 functions as part of a specific Protein Phosphatase 4 complex ($PP4^{SMK-1}$). Loss of $PP4^{SMK-1}$ hinders transcriptional initiation at several DAF-16-activated genes, predominantly by impairing RNA polymerase II recruitment to their promoters. Search for the relevant substrate of $PP4^{SMK-1}$ by phosphoproteomics identified the conserved transcriptional regulator SPT-5/SUPT5H, whose knockdown phenocopies the loss of $PP4^{SMK-1}$. Phosphoregulation of SPT-5 is known to control transcriptional events such as elongation and termination. Here we also show that transcription initiating events are influenced by the phosphorylation status of SPT-5, particularly at DAF-16 target genes where transcriptional initiation appears rate limiting, rendering $PP4^{SMK-1}$ crucial for many of DAF-16's physiological roles.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Zinc transporters maintain longevity by influencing insulin/IGF-1 activity in *Caenorhabditis elegans*

Adequate dietary intake of essential metals such as zinc is important for maintaining homeostasis. Abnormal zinc intake in *Caenorhabditis elegans* has been shown to increase or decrease normal lifespan by influencing the insulin/IGF-1 pathway. Distribution of zinc is achieved by a family of highly conserved zinc transport proteins (ZIPT in *C. elegans*). This study investigated the role of the *zipt* family of genes and showed that depletion of individual *zipt* genes results in a decreased lifespan. Moreover, *zipt-16* and *zipt-17* mutants synthetically interact with the insulin/IGF cofactors *daf-16* and *skn-1*, and cause abnormal localisation of DAF-16. This study suggests that the *zipt* family of genes are required for maintaining normal lifespan through influencing the insulin/IGF-1 pathway.

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Understanding muscle regenerative decline with aging: new approaches to bring back youthfulness to aged stem cells

Pura Muñoz-Cánoves, Joana Neves, Pedro Sousa-Victor

Aging is characterized by the progressive dysfunction of most tissues and organs, which has been linked to the regenerative decline of their resident stem cells over time. Skeletal muscle provides a stark example of this decline. Its stem cells, also called satellite cells, sustain muscle regeneration throughout life, but at advanced age they fail for largely undefined reasons. Here, we discuss current understanding of the molecular processes regulating satellite cell maintenance throughout life and how age-related failure of these processes contributes to muscle aging. We also highlight the emerging field of rejuvenating biology to restore features of youthfulness in satellite cells, with the ultimate goal of slowing down or reversing the age-related decline in muscle regeneration.

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Probiotic *Bacillus subtilis* Protects against α-Synuclein Aggregation in *C. elegans*

Recent discoveries have implicated the gut microbiome in the progression and severity of Parkinson's disease; however, how gut bacteria affect such neurodegenerative disorders remains unclear. Here, we report that the *Bacillus subtilis* probiotic strain PXN21 inhibits α-synuclein aggregation and clears preformed aggregates in an established *Caenorhabditis elegans* model of synucleinopathy. This protection is seen in young and aging animals and is partly mediated by DAF-16. Multiple *B. subtilis* strains trigger the protective effect via both spores and vegetative cells, partly due to a biofilm formation in the gut of the worms and the release of bacterial metabolites. We identify several host metabolic pathways differentially regulated in response to probiotic exposure, including sphingolipid metabolism. We further demonstrate functional roles of the sphingolipid metabolism genes *lagr-1*, *asm-3*, and *sptl-3* in the anti-aggregation effect. Our findings provide a basis for exploring the disease-modifying potential of *B. subtilis* as a dietary supplement.

REVIEWS/COMMENTS/ METHODS/EDITORIALS

RTB101 and immune function in the elderly: Interpreting an unsuccessful clinical trial

Matt Kaeberlein ✉

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https://doi.org/10.1016/j.tma.2020.01.002

Abstract

The biopharmaceutical company resTORbio, Inc. Recently announced termination of a phase 3 clinical trial evaluating the ability of the drug RTB101 to improve immune function in the elderly. The company reported that the first stage of the PROTECTOR1 trial did not meet its primary endpoint for reducing clinically symptomatic respiratory illness in healthy older adults. Although RTB101 has been described as an inhibitor of the mechanistic target of rapamycin (mTOR), the PROTECTOR1 trial was not a test of the geroscience hypothesis. Unlike the geroprotective compound rapamycin, RTB101 has not been found to increase lifespan or delay age-related functional or molecular phenotypes in pre-clinical animal models. RTB101 was first developed as an inhibitor of phosphoinositide-3-kinase (PI3K) with secondary inhibitory effects on mTOR. It's ATP-competitive mechanism of action is distinct from the allosteric inhibition by rapamycin and does not specifically target mTOR complex 1 over mTOR complex 2. Clinical development of rapamycin and other specific mTOR complex 1 inhibitors to target age-related indications continues to be robust, and there is growing momentum for translational geroscience, with numerous clinical trials planned or ongoing in this area.

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The Urgent Need for International Action for Anti-aging and Disease Prevention

Robert Chunhua Zhao[1, 3, *], Ilia Stambler[2, 3, *]

There is a growing consensus that researching and developing therapeutic interventions into degenerative aging processes is a necessary condition for improving the health and longevity of the rapidly aging global population Thus, the research and development of therapies against degenerative aging processes (anti-aging) and for prevention of major aging-related diseases is a necessary condition for alleviating the severe economic, healthcare and humanitarian challenges of the global aging society And therefore, promoting the research and development in the field of anti-aging and aging-related disease prevention is becoming an urgent national and international task [1,2] How can the field of anti-aging and disease prevention be promoted globally to solve the challenge of bringing effective, safe and accessible anti-aging and preventive therapies to the world as soon as possible? A significant further step was taken toward the solution of this challenge with the establishment of the new Executive Committee on Anti-aging and Disease Prevention, a joint effort of UNESCO and China World Peace Foundation.

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mTOR at the nexus of nutrition, growth, ageing and disease

Grace Y. Liu & David M. Sabatini

Nature Reviews Molecular Cell Biology (2020) | Cite this article

118 Altmetric | Metrics

Abstract

The mTOR pathway integrates a diverse set of environmental cues, such as growth factor signals and nutritional status, to direct eukaryotic cell growth. Over the past two and a half decades, mapping of the mTOR signalling landscape has revealed that mTOR controls biomass accumulation and metabolism by modulating key cellular processes, including protein synthesis and autophagy. Given the pathway's central role in maintaining cellular and physiological homeostasis, dysregulation of mTOR signalling has been implicated in metabolic disorders, neurodegeneration, cancer and ageing. In this Review, we highlight recent advances in our understanding of the complex regulation of the mTOR pathway and discuss its function in the context of physiology, human disease and pharmacological intervention.

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Protecting the Aging Genome

Mounting evidence suggests that DNA damage plays a central role in aging. Multiple tiers of defense have evolved to reduce the accumulation of DNA damage, including reducing damaging molecules, repairing DNA damage, and inducing senescence or apoptosis in response to persistent DNA damage. Mutations in or failure of these pathways can lead to accelerated or premature aging and age-related decline in vital organs, supporting the hypothesis that maintaining a pristine genome is paramount for human health. Understanding how we cope with DNA damage could inform on the aging process and further on how deficient DNA maintenance manifests in age-related phenotypes. This knowledge may lead to the development of novel interventions promoting healthspan.

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FEBS J. 2020 Jan 8. doi: 10.1111/febs.15205. [Epub ahead of print]

Poor old pores-The challenge of making and maintaining nuclear pore complexes in aging.

Rempel IL[1], Steen A[1], Veenhoff LM[1].

⊕ Author information

Abstract

The nuclear pore complex (NPC) is the sole gateway to the nuclear interior, and its function is essential to all eukaryotic life. Controlling the functionality of NPCs is a tremendous challenge for cells. Firstly, NPCs are large structures, and their complex assembly does occasionally go awry. Secondly, once assembled, some components of the NPC persist for an extremely long time and, as a result, are susceptible to accumulate damage. Lastly, a significant proportion of the NPC is composed of intrinsically disordered proteins that are prone to aggregation. In this review, we summarize how the quality of NPCs is guarded in young cells and discuss the current knowledge on the fate of NPCs during normal aging in different tissues and organisms. We discuss the extent to which current data supports a hypothesis that NPCs are poorly maintained during aging of nondividing cells, while in dividing cells the main challenge is related to the assembly of new NPCs. Our survey of current knowledge points toward NPC quality control as an important node in aging of both dividing and nondividing cells. Here, the loss of protein homeostasis during aging is central and the NPC appears to both be impacted by, and to drive, this process.

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The lysosome as a cellular centre for signalling, metabolism and quality control

Rosalie E. Lawrence & Roberto Zoncu

Nature Cell Biology **21**, 133–142(2019) | Cite this article

13k Accesses | **39** Citations | **68** Altmetric | Metrics

Abstract

Long known as terminal degradation stations, lysosomes have emerged as sophisticated signalling centres that govern cell growth, division and differentiation. Lysosomes interface physically and functionally with other organelles, and the master regulator mechanistic target of rapamycin complex 1 kinase is activated on lysosomes in response to nutrient and growth factor inputs. Lysosomes also enable autophagy, a 'self-eating' process essential for quality control and stress adaptation. Faulty execution of lysosomal growth and catabolic programmes drives cancer, neurodegeneration and age-related diseases.

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Mitophagy and DNA damage signaling in human aging.

Babbar M, et al. Mech Ageing Dev. 2020.
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Abstract

Aging is associated with multiple human pathologies. In the past few years mitochondrial homeostasis has been well correlated with age-related disorders and longevity. Mitochondrial homeostasis involves generation, biogenesis and removal of dysfunctional mitochondria via mitophagy. Mitophagy is regulated by various mitochondrial and extra-mitochondrial factors including morphology, oxidative stress and DNA damage. For decades, DNA damage and inefficient DNA repair have been considered as major determinants for age-related disorders. Although defects in DNA damage recognition and repair and mitophagy are well documented to be major factors in age-associated diseases, interactivity between these is poorly understood. Mitophagy efficiency decreases with age leading to accumulation of dysfunctional mitochondria enhancing the severity of age-related disorders including neurodegenerative diseases, inflammatory diseases, cancer, diabetes and many more. Therefore, mitophagy is being targeted for intervention in age-associated disorders. NAD+ supplementation has emerged as one intervention to target both defective DNA repair and mitophagy. In this review, we discuss the molecular signaling pathways involved in regulation of DNA damage and repair and of mitophagy, and we highlight the opportunities for clinical interventions targeting these processes to improve the quality of life during aging.

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NAD^+ homeostasis in health and disease

Elena Katsyuba, Mario Romani, Dina Hofer & Johan Auwerx

The conceptual evolution of nicotinamide adenine dinucleotide (NAD^+) from being seen as a simple metabolic cofactor to a pivotal cosubstrate for proteins regulating metabolism and longevity, including the sirtuin family of protein deacylases, has led to a new wave of scientific interest in NAD^+. NAD^+ levels decline during ageing, and alterations in NAD^+ homeostasis can be found in virtually all age-related diseases, including neurodegeneration, diabetes and cancer. In preclinical settings, various strategies to increase NAD^+ levels have shown beneficial effects, thus starting a competitive race to discover marketable NAD^+ boosters to improve healthspan and lifespan. Here, we review the basics of NAD^+ biochemistry and metabolism, and its roles in health and disease, and we discuss current challenges and the future translational potential of NAD^+ research.

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Senolytics: A Translational Bridge Between Cellular Senescence and Organismal Aging

 Harikrishnan Thoppil[1,2] and Karl Riabowol[1,2*]

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[2]Arnie Charbonneau Cancer Institute, Department of Oncology, University of Calgary, Calgary, AB, Canada

Aging is defined as a progressive decrease in physiological function accompanied by a steady increase in mortality. The antagonistic pleiotropy theory proposes that aging is largely due to the natural selection of genes and pathways that increase fitness and decrease mortality early in life but contribute to deleterious effects and pathologies later in life. Cellular senescence is one such mechanism, which results in a permanent cell cycle arrest that has been described as a mechanism to limit cancer cell growth. However, recent studies have also suggested a dark side of senescence in which a build-up of senescent cells with age leads to increased inflammation due to a senescence-associated secretory phenotype (SASP). This phenotype that includes many cytokines promotes tumorigenesis and can exhaust the pool of immune cells in the body. Studies clearing senescent cells from mice using the p16-based transgene INK-ATTAC have shown that senescent cells can impact both organismal aging and lifespan. Here we discuss these advances that have resulted in the development of a whole new class of compounds known as senolytics, some of which are currently undergoing clinical trials in humans for treating a variety of age-related pathologies such as osteoarthritis.

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Rejuvenating subventricular zone neurogenesis in the aging brain

Ronald R Cutler [1], Erzsebet Kokovay [1, 2] ✉

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https://doi.org/10.1016/j.coph.2019.10.005

Neural stem cells exist in specialized regions of the brain and have the capacity to give rise to neurons and glia over the lifespan. The process of giving rise to new neurons, also known as neurogenesis, is thought to be important in cognition and certain types of brain repair. However, during aging, neural stem cell number and function is reduced resulting in fewer new neurons and declines in learning, memory and repair. Recently, research has approached this problem through the lens of rejuvenation that now has produced several strategies, from dietary to pharmacological interventions, to restore functional neurogenesis that resembles the youthful brain. Here, we outline aging in the subventricular zone neurogenic niche, review the multiple modalities of rejuvenation strategies, and propose next steps for future studies to approach translational outcomes.

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The future of stem cell therapies for Parkinson disease

Malin Parmar[1,2]*, *Shane Grealish*[1,2] *and Claire Henchcliffe*[3]

Abstract | Cell-replacement therapies have long been an attractive prospect for treating Parkinson disease. However, the outcomes of fetal tissue-derived cell transplants in individuals with Parkinson disease have been variable, in part owing to the limitations of fetal tissue as a cell source, relating to its availability and the lack of possibility for standardization and to variation in methods. Advances in developmental and stem cell biology have allowed the development of cell-replacement therapies that comprise dopamine neurons derived from human pluripotent stem cells, which have several advantages over fetal cell-derived therapies. In this Review, we critically assess the potential trajectory of this line of translational and clinical research and address its possibilities and current limitations and the broader range of Parkinson disease features that dopamine cell replacement based on generating neurons from human pluripotent stem cells could effectively treat in the future.

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Why do bats live so long?—Possible molecular mechanisms

Contrasting with several theories of ageing, bats are mammals with remarkable longevity despite their high metabolic rate, living on average three times more than other mammals of equal size. The question of how bats live a long time has attracted considerable attention, and they have thus been related to immortal fantasy characters like Dracula in the novel by Bram Stoker. Several ecological and physiological features, such as reduction in mortality risks, delayed sexual maturation and hibernation, have been linked to bats' long lifespan. However, there is still very little information about the molecular mechanisms associated with the longevity of bats. In this regard, the present work tries to summarize current knowledge about how bats can live for so long, taking into consideration nutritional factors, oxidative metabolism, protein homeostasis, stress resistance, DNA repair, mitochondrial physiology and cancer resistance.

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HEALTHY LIFE EXTENSION SOCIETY

Comp Biochem Physiol A Mol Integr Physiol. 2020 Jan 16;242:110658. doi: 10.1016/j.cbpa.2020.110658. [Epub ahead of print]

A dose of experimental hormesis: When mild stress protects and improves animal performance.

Berry R 3rd[1], López-Martínez G[2].

Author information

Abstract

The adaptive response characterized by a biphasic curve is known as hormesis. In a hormesis framework, exposure to low doses leads to protective and beneficial responses while exposures to high doses are damaging and detrimental. Comparative physiologists have studied hormesis for over a century, but our understanding of hormesis is fragmented due to rifts in consensus and taxonomic-specific terminology. Hormesis has been and is currently known by multiple names; preconditioning, conditioning, pretreatment, cross tolerance, adaptive homeostasis, and rapid stress hardening (mostly low temperature: rapid cold hardening). These are the most common names used to describe adaptive stress responses in animals. These responses are mechanistically similar, while having stress-specific responses, but they all can fall under the umbrella of hormesis. Here we review how hormesis studies have revealed animal performance benefits in response to changes in oxygen, temperature, ionizing radiation, heavy metals, pesticides, dehydration, gravity, and crowding. And how almost universally, hormetic responses are characterized by increases in performance that include either increases in reproduction, longevity, or both. And while the field can benefit from additional mechanistic work, we know that many of these responses are rooted in increases of antioxidants and oxidative stress protective mechanisms; including heat shock proteins. There is a clear, yet not fully elucidated, overlap between hormesis and the preparation for oxidative stress theory; which predicts part of the responses associated with hormesis. We discuss this, and the need for additional work into animal hormetic effects particularly focusing on the cost of hormesis.

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Exp Gerontol. 2020 Jan 16:110841. doi: 10.1016/j.exger.2020.110841. [Epub ahead of print]

Kynurenine pathway, NAD^+ synthesis, and mitochondrial function: Targeting tryptophan metabolism to promote longevity and healthspan.

Castro-Portuguez R[1], Sutphin GL[2].

⊕ Author information

Abstract

Aging is characterized by a progressive decline in the normal physiological functions of an organism, ultimately leading to mortality. Nicotinamide adenine dinucleotide (NAD^+) is an essential cofactor that plays a critical role in mitochondrial energy production as well as many enzymatic redox reactions. Age-associated decline in NAD^+ is implicated as a driving factor in several categories of age-associated disease, including metabolic and neurodegenerative disease, as well as deficiency in the mechanisms of cellular defense against oxidative stress. The kynurenine metabolic pathway is the sole de novo NAD^+ biosynthetic pathway, generating NAD^+ from ingested tryptophan. Altered kynurenine pathway activity is associated with both aging and a variety of age-associated diseases. Kynurenine pathway interventions can extend lifespan in both fruit flies and nematodes, and altered NAD^+ metabolism represents one potential mediating mechanism. Recent studies demonstrate that supplementation with NAD^+ or NAD^+-precursors increase longevity and promote healthy aging in fruit flies, nematodes, and mice. NAD^+ levels and the intrinsic relationship to mitochondrial function have been widely studied in the context of aging. Mitochondrial function and dynamics have both been are implicated in longevity determination in a range of organisms from yeast to humans, at least in part due to their intimate link to regulating an organism's cellular energy economy and capacity to resist oxidative stress. Recent findings support the idea that complex communication between the mitochondria and the nucleus orchestrates a series of events and stress responses involving mitophagy, mitochondrial number, mitochondrial unfolded protein response (UPR^{mt}), and mitochondria fission and fusion events. In this review, we discuss how mitochondrial morphological changes and dynamics operate during aging, and how altered metabolism of tryptophan to NAD^+ through the kynurenine pathway interacts with these processes.

OTHER RESEARCH & REVIEWS

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Fresh from the biotech pipeline—2019

Chris Morrison

Nature Biotechnology (2020) | Cite this article

10 Altmetric | Metrics

The biopharmaceutical industry's positive regulatory momentum carried on through 2019, despite an early-year government shutdown, a data manipulation scandal around a high-profile approval, and many months without permanent leadership at the FDA.

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Proc Natl Acad Sci U S A. 2020 Jan 24. pii: 201909378. doi: 10.1073/pnas.1909378117. [Epub ahead of print]

Precision medicine integrating whole-genome sequencing, comprehensive metabolomics, and advanced imaging.

Hou YC[1], Yu HC[1], Martin R[1], Cirulli ET[1], Schenker-Ahmed NM[1,2], Hicks M[1], Cohen IV[1,3], Jönsson TJ[4], Heister R[1], Napier L[1], Swisher CL[1], Dominguez S[1], Tang H[1], Li W[5], Perkins BA[1], Barea J[1], Rybak C[1], Smith E[1], Duchicela K[1], Doney M[1], Brar P[1,5], Hernandez N[1], Kirkness EF[5], Kahn AM[1,6], Venter JC[1,5], Karow DS[1,2], Caskey CT[7,8].

⊕ Author information

Abstract

Genome sequencing has established clinical utility for rare disease diagnosis. While increasing numbers of individuals have undergone elective genome sequencing, a comprehensive study surveying genome-wide disease-associated genes in adults with deep phenotyping has not been reported. Here we report the results of a 3-y precision medicine study with a goal to integrate whole-genome sequencing with deep phenotyping. A cohort of 1,190 adult participants (402 female [33.8%]; mean age, 54 y [range 20 to 89+]; 70.6% European) had whole-genome sequencing, and were deeply phenotyped using metabolomics, advanced imaging, and clinical laboratory tests in addition to family/medical history. Of 1,190 adults, 206 (17.3%) had at least 1 genetic variant with pathogenic (P) or likely pathogenic (LP) assessment that suggests a predisposition of genetic risk. A multidisciplinary clinical team reviewed all reportable findings for the assessment of genotype and phenotype associations, and 137 (11.5%) had genotype and phenotype associations. A high percentage of genotype and phenotype associations (>75%) was observed for dyslipidemia (n = 24), cardiomyopathy, arrhythmia, and other cardiac diseases (n = 42), and diabetes and endocrine diseases (n = 17). A lack of genotype and phenotype associations, a potential burden for patient care, was observed in 69 (5.8%) individuals with P/LP variants. Genomics and metabolomics associations identified 61 (5.1%) heterozygotes with phenotype manifestations affecting serum metabolite levels in amino acid, lipid and cofactor, and vitamin pathways. Our descriptive analysis provides results on the integration of whole-genome sequencing and deep phenotyping for clinical assessments in adults.

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Blood contains circulating cell-free respiratory competent mitochondria

Mitochondria are considered as the power-generating units of the cell due to their key role in energy metabolism and cell signaling. However, mitochondrial components could be found in the extracellular space, as fragments or encapsulated in vesicles. In addition, this intact organelle has been recently reported to be released by platelets exclusively in specific conditions. Here, we demonstrate for the first time, that blood preparation with resting platelets, contains whole functional mitochondria in normal physiological state. Likewise, we show, that normal and tumor cultured cells are able to secrete their mitochondria. Using serial centrifugation or filtration followed by polymerase chain reaction-based methods, and Whole Genome Sequencing, we detect extracellular full-length mitochondrial DNA in particles over 0.22 μm holding specific mitochondrial membrane proteins. We identify these particles as intact cell-free mitochondria using fluorescence-activated cell sorting analysis, fluorescence microscopy, and transmission electron microscopy. Oxygen consumption analysis revealed that these mitochondria are respiratory competent. In view of previously described mitochondrial potential in intercellular transfer, this discovery could greatly widen the scope of cell-cell communication biology. Further steps should be developed to investigate the potential role of mitochondria as a signaling organelle outside the cell and to determine whether these circulating units could be relevant for early detection and prognosis of various diseases.

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Comparing meta-analyses and preregistered multiple-laboratory replication projects

Amanda Kvarven, Eirik Strømland & Magnus Johannesson

Many researchers rely on meta-analysis to summarize research evidence. However, there is a concern that publication bias and selective reporting may lead to biased meta-analytic effect sizes. We compare the results of meta-analyses to large-scale preregistered replications in psychology carried out at multiple laboratories. The multiple-laboratory replications provide precisely estimated effect sizes that do not suffer from publication bias or selective reporting. We searched the literature and identified 15 meta-analyses on the same topics as multiple-laboratory replications. We find that meta-analytic effect sizes are significantly different from replication effect sizes for 12 out of the 15 meta-replication pairs. These differences are systematic and, on average, meta-analytic effect sizes are almost three times as large as replication effect sizes. We also implement three methods of correcting meta-analysis for bias, but these methods do not substantively improve the meta-analytic results.

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mTORC1 directly inhibits AMPK to promote cell proliferation under nutrient stress

Highly conserved signalling pathways controlled by mammalian target of rapamycin (mTOR) and AMP-activated protein kinase (AMPK) are central to cellular metabolism and cell proliferation[1,2], and their dysregulation is implicated in the pathogenesis of major human diseases such as cancer and type 2 diabetes. AMPK pathways leading to reduced cell proliferation are well established and, in part, act through inhibition of TOR complex 1 (TORC1) activity. Here we demonstrate reciprocal regulation, specifically that TORC1 directly downregulates AMPK signalling by phosphorylating the evolutionarily conserved residue S367 in the fission yeast AMPK catalytic subunit Ssp2 and AMPK α1 S347 and α2 S345 in the mammalian homologs, which is associated with reduced phosphorylation of activation loop T172. Genetic or pharmacological inhibition of TORC1 signalling led to AMPK activation in the absence of increased AMP/ATP ratios, which under nutrient stress conditions was associated with growth limitation in both yeast and human cell cultures. Our findings reveal fundamental bidirectional regulation between two major metabolic signalling networks and uncover new opportunities for cancer treatment strategies aimed at suppressing cell proliferation in the nutrient-poor tumour microenvironment.

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High-Throughput PIXE as an Essential Quantitative Assay for Accurate Metalloprotein Structural Analysis: Development and Application

Metalloproteins comprise over one-third of proteins, with approximately half of all enzymes requiring metal to function. Accurate identification of these metal atoms and their environment is a prerequisite to understanding biological mechanism. Using ion beam analysis through particle induced X-ray emission (PIXE), we have quantitatively identified the metal atoms in 30 previously structurally characterized proteins using minimal sample volume and a high-throughput approach. Over half of these metals had been misidentified in the deposited structural models. Some of the PIXE detected metals not seen in the models were explainable as artifacts from promiscuous crystallization reagents. For others, using the correct metal improved the structural models. For multinuclear sites, anomalous diffraction signals enabled the positioning of the correct metals to reveal previously obscured biological information. PIXE is insensitive to the chemical environment, but coupled with experimental diffraction data deposited alongside the structural model it enables validation and potential remediation of metalloprotein models, improving structural and, more importantly, mechanistic knowledge.

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Maintaining Iron Homeostasis Is the Key Role of Lysosomal Acidity for Cell Proliferation

The lysosome is an acidic multi-functional organelle with roles in macromolecular digestion, nutrient sensing, and signaling. However, why cells require acidic lysosomes to proliferate and which nutrients become limiting under lysosomal dysfunction are unclear. To address this, we performed CRISPR-Cas9-based genetic screens and identified cholesterol biosynthesis and iron uptake as essential metabolic pathways when lysosomal pH is altered. While cholesterol synthesis is only necessary, iron is both necessary and sufficient for cell proliferation under lysosomal dysfunction. Remarkably, iron supplementation restores cell proliferation under both pharmacologic and genetic-mediated lysosomal dysfunction. The rescue was independent of metabolic or signaling changes classically associated with increased lysosomal pH, uncoupling lysosomal function from cell proliferation. Finally, our experiments revealed that lysosomal dysfunction dramatically alters mitochondrial metabolism and hypoxia inducible factor (HIF) signaling due to iron depletion. Altogether, these findings identify iron homeostasis as the key function of lysosomal acidity for cell proliferation.

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Targeting of temperate phages drives loss of type I CRISPR–Cas systems

On infection of their host, temperate viruses that infect bacteria (bacteriophages; hereafter referred to as phages) enter either a lytic or a lysogenic cycle. The former results in lysis of bacterial cells and phage release (resulting in horizontal transmission), whereas lysogeny is characterized by the integration of the phage into the host genome, and dormancy (resulting in vertical transmission)[1]. Previous co-culture experiments using bacteria and mutants of temperate phages that are locked in the lytic cycle have shown that CRISPR–Cas systems can efficiently eliminate the invading phages[2,3]. Here we show that, when challenged with wild-type temperate phages (which can become lysogenic), type I CRISPR–Cas immune systems cannot eliminate the phages from the bacterial population. Furthermore, our data suggest that, in this context, CRISPR–Cas immune systems are maladaptive to the host, owing to the severe immunopathological effects that are brought about by imperfect matching of spacers to the integrated phage sequences (prophages). These fitness costs drive the loss of CRISPR–Cas from bacterial populations, unless the phage carries anti-CRISPR (acr) genes that suppress the immune system of the host. Using bioinformatics, we show that this imperfect targeting is likely to occur frequently in nature. These findings help to explain the patchy distribution of CRISPR–Cas immune systems within and between bacterial species, and highlight the strong selective benefits of phage-encoded acr genes for both the phage and the host under these circumstances.

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Will Artificial Intelligence for Drug Discovery Impact Clinical Pharmacology?

Alex Zhavoronkov, Quentin Vanhaelen, Tudor I. Oprea

As the field of artificial intelligence and machine learning (AI/ML) for drug discovery is rapidly advancing, we address the question "what is the impact of recent AI/ML trends in the area of Clinical Pharmacology". We address difficulties and AI/ML developments for target identification, their use in generative chemistry for small molecule drug discovery, and the potential role of AI/ML in clinical trial outcome evaluation. We briefly discuss current trends in the use of AI/ML in healthcare and the impact of AI/ML context of the daily practice of clinical pharmacologists.

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Axes of a revolution: challenges and promises of big data in healthcare

Smadar Shilo[1,2,3,4], Hagai Rossman [1,2,4] and Eran Segal [1,2*]

Health data are increasingly being generated at a massive scale, at various levels of phenotyping and from different types of resources. Concurrent with recent technological advances in both data-generation infrastructure and data-analysis methodologies, there have been many claims that these events will revolutionize healthcare, but such claims are still a matter of debate. Addressing the potential and challenges of big data in healthcare requires an understanding of the characteristics of the data. Here we characterize various properties of medical data, which we refer to as 'axes' of data, describe the considerations and tradeoffs taken when such data are generated, and the types of analyses that may achieve the tasks at hand. We then broadly describe the potential and challenges of using big data in healthcare resources, aiming to contribute to the ongoing discussion of the potential of big data resources to advance the understanding of health and disease.

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A brief history of human disease genetics

A primary goal of human genetics is to identify DNA sequence variants that influence biomedical traits, particularly those related to the onset and progression of human disease. Over the past 25 years, progress in realizing this objective has been transformed by advances in technology, foundational genomic resources and analytical tools, and by access to vast amounts of genotype and phenotype data. Genetic discoveries have substantially improved our understanding of the mechanisms responsible for many rare and common diseases and driven development of novel preventative and therapeutic strategies. Medical innovation will increasingly focus on delivering care tailored to individual patterns of genetic predisposition.

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Mechanisms of tissue and cell-type specificity in heritable traits and diseases

Idan Hekselman[1] *and Esti Yeger-Lotem* [1,2]*

Abstract | Hundreds of heritable traits and diseases that are caused by germline aberrations in ubiquitously expressed genes manifest in a remarkably limited number of cell types and tissues across the body. Unravelling mechanisms that govern their tissue-specific manifestations is critical for our understanding of disease aetiologies and may direct efforts to develop treatments. Owing to recent advances in high-throughput technologies and open resources, data and tools are now available to approach this enigmatic phenomenon at large scales, both computationally and experimentally. Here, we discuss the large prevalence of tissue-selective traits and diseases, describe common molecular mechanisms underlying their tissue-selective manifestation and present computational strategies and publicly available resources for elucidating the molecular basis of their genotype–phenotype relationships.

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Gene size matters: What determines gene length in the human genome?

Inês Lopes, Gulam Altab, Priyanka Raina, João Pedro de Magalhães

While it is expected for gene length to be influenced by factors such as intron number and evolutionary conservation, we have yet to fully understand the connection between gene length and function in the human genome.

In this study, we show that, as expected, there is a strong positive correlation between gene length and the number of SNPs, introns and protein size. Amongst tissue specific genes, we find that the longest genes are expressed in blood vessels, nerve, thyroid, cervix uteri and brain, while the smallest genes are expressed within the pancreas, skin, stomach, vagina and testis. We report, as shown previously, that natural selection suppresses changes for genes with longer lengths and promotes changes for smaller genes. We also observed that longer genes have a significantly higher number of co-expressed genes and protein-protein interactions. In the functional analysis, we show that bigger genes are often associated with neuronal development, while smaller genes tend to play roles in skin development and in the immune system. Furthermore, pathways related to cancer, neurons and heart diseases tend to have longer genes, with smaller genes being present in pathways related to immune response and neurodegenerative diseases.

We hypothesise that longer genes tend to be associated with functions that are important early in life, while smaller genes play a role in functions that are important throughout the organisms' whole life, like the immune system which require fast responses.

Heales
HEALTHY LIFE EXTENSION SOCIETY

The predictive power of the microbiome exceeds that of genome-wide association studies in the discrimination of complex human disease

Braden T Tierney, Yixuan He, George M Church, Eran Segal, Aleksandar D Kostic, Chirag J Patel

Over the past decade, studies of the human genome and microbiome have deepened our understanding of the connections between human genes, environments, microbes, and disease. For example, the sheer number of indicators of the microbiome and human genetic common variants associated with disease has been immense, but clinical utility has been elusive. Here, we compared the predictive capabilities of the human microbiome versus human genomic common variants across 13 common diseases. We concluded that microbiomic indicators outperform human genetics in predicting host phenotype (overall Microbiome-Association-Study [MAS] area under the curve [AUC] = 0.79 [SE = 0.03], overall Genome-Wide-Association-Study [GWAS] AUC = 0.67 [SE = 0.02]). Our results, while preliminary and focused on a subset of the totality of disease, demonstrate the relative predictive ability of the microbiome, indicating that it may outperform human genetics in discriminating human disease cases and controls. They additionally motivate the need for population-level microbiome sequencing resources, akin to the UK Biobank, to further improve and reproduce metagenomic models of disease.

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Are drug targets with genetic support twice as likely to be approved? Revised estimates of the impact of genetic support for drug mechanisms on the probability of drug approval

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Despite strong vetting for disease activity, only 10% of candidate new molecular entities in early stage clinical trials are eventually approved. Analyzing historical pipeline data, Nelson et al. 2015 (Nat. Genet.) concluded pipeline drug targets with human genetic evidence of disease association are twice as likely to lead to approved drugs. Taking advantage of recent clinical development advances and rapid growth in GWAS datasets, we extend the original work using updated data, test whether genetic evidence predicts future successes and introduce statistical models adjusting for target and indication-level properties. Our work confirms drugs with genetically supported targets were more likely to be successful in Phases II and III. When causal genes are clear (Mendelian traits and GWAS associations linked to coding variants), we find the use of human genetic evidence increases approval by greater than two-fold, and, for Mendelian associations, the positive association holds prospectively. Our findings suggest investments into genomics and genetics are likely to be beneficial to companies deploying this strategy.

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Discovering the anticancer potential of non-oncology drugs by systematic viability profiling

Anticancer uses of non-oncology drugs have occasionally been found, but such discoveries have been serendipitous. We sought to create a public resource containing the growth-inhibitory activity of 4,518 drugs tested across 578 human cancer cell lines. We used PRISM (profiling relative inhibition simultaneously in mixtures), a molecular barcoding method, to screen drugs against cell lines in pools. An unexpectedly large number of non-oncology drugs selectively inhibited subsets of cancer cell lines in a manner predictable from the molecular features of the cell lines. Our findings include compounds that killed by inducing phosphodiesterase 3A-Schlafen 12 complex formation, vanadium-containing compounds whose killing depended on the sulfate transporter SLC26A2, the alcohol dependence drug disulfiram, which killed cells with low expression of metallothioneins, and the anti-inflammatory drug tepoxalin, which killed via the multidrug resistance protein ATP-binding cassette subfamily B member 1 (ABCB1). The PRISM drug repurposing resource (https://depmap.org/repurposing) is a starting point to develop new oncology therapeutics, and more rarely, for potential direct clinical translation.

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Temporal inhibition of autophagy reveals segmental reversal of ageing with increased cancer risk.

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Abstract

Autophagy is an important cellular degradation pathway with a central role in metabolism as well as basic quality control, two processes inextricably linked to ageing. A decrease in autophagy is associated with increasing age, yet it is unknown if this is causal in the ageing process, and whether autophagy restoration can counteract these ageing effects. Here we demonstrate that systemic autophagy inhibition induces the premature acquisition of age-associated phenotypes and pathologies in mammals. Remarkably, autophagy restoration provides a near complete recovery of morbidity and a significant extension of lifespan; however, at the molecular level this rescue appears incomplete. Importantly autophagy-restored mice still succumb earlier due to an increase in spontaneous tumour formation. Thus, our data suggest that chronic autophagy inhibition confers an irreversible increase in cancer risk and uncovers a biphasic role of autophagy in cancer development being both tumour suppressive and oncogenic, sequentially.

Multiyear Follow-up of AAV5-hFVIII-SQ Gene Therapy for Hemophilia A

BACKGROUND Adeno-associated virus (AAV)–mediated gene therapy is under investigation as a therapeutic option for persons with hemophilia A. Efficacy and safety data include 3 years of follow-up after a single administration of AAV5-hFVIII-SQ.

METHODS We report durable efficacy, long-term safety, and clinical and biologic results in 15 adults with severe hemophilia A (factor VIII level, ≤1 IU per deciliter) who had received a single infusion of AAV5-hFVIII-SQ at various dose levels. We evaluated the factor VIII level, annualized rate of bleeding events, use of factor VIII, safety, expression kinetics, and biologic markers of AAV transduction for up to 3 years.

RESULTS Three years after infusion, two participants (one who had received 6×10^{12} vector genomes [vg] per kilogram of body weight and one who had received 2×10^{13} vg per kilogram) had factor VIII expression of less than 1 IU per deciliter, as assessed on chromogenic assay. Seven participants (who had received 6×10^{13} vg per kilogram) had a median factor VIII expression of 20 IU per deciliter; the median number of annualized treated bleeding events was 0, and the median use of exogenous factor VIII was reduced from 138.5 infusions to 0 infusions per year. Bleeding in all target joints (major joints with ≥3 bleeding events within 6 months) in this cohort resolved (≤2 bleeding events within 12 months). Two years after infusion, six participants (who had received 4×10^{13} vg per kilogram) had a median factor VIII expression of 13 IU per deciliter; the median annualized rate of bleeding events was 0, and the median use of factor VIII was reduced from 155.5 infusions to 0.5 infusions per year. Bleeding in target joints resolved in five of six participants. The factor VIII pharmacodynamic profiles reflected cellular turnover in the blood and molecular events leading to episomal DNA stabilization for persistent expression, findings that are consistent with previous observations in two model systems. Transgene-derived human factor VIII (hFVIII) protein activity mirrored native hFVIII in hemostatic ability. No inhibitor development, thromboses, deaths, or persistent changes in liver-function tests were observed.

CONCLUSIONS Gene therapy with AAV5-hFVIII-SQ vector in participants with hemophilia A resulted in sustained, clinically relevant benefit, as measured by a substantial reduction in annualized rates of bleeding events and complete cessation of prophylactic factor VIII use in all participants who had received 4×10^{13} vg per kilogram or 6×10^{13} vg per kilogram of the gene therapy. (Funded by BioMarin Pharmaceutical; ClinicalTrials.gov number, NCT02576795; EudraCT number, 2014-003880-38.)