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Scientific News
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Sven Bulterijs

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Biogen, Eisai throw out remaining Alzheimer's BACE hope

by Ben Adams | Sep 13, 2019 8:55am

Biogen and Eisai's last major, late-stage attempt at stopping Alzheimer's using a BACE inhibitor has ended up on the trash pile. This comes after the Data Safety Monitoring Board raised safety concerns over the drug. (Biogen)

One of the last major, late-stage attempt at stopping Alzheimer's disease (AD) using a BACE inhibitor has ended up on the trash pile with so many others.

Earlier this year, Biogen and partner Eisai canned the remaining phase 3 trial of aducanumab, their first BACE asset aimed at AD, effectively killing off the program after it turned out to be a dud.

This came after much hype and expectation that it could be a pivotal treatment in treating the memory-wasting disease. There was another, however: elenbecestat, a second beta amyloid drug from the pair they hoped (though this hope has been diminishing in recent times) could, somehow, pick up where aducanumab had fallen.

Alzheimer's setbacks have prompted $39bn of market cap losses this year

Amy Brown

Edwin Elmhirst

Neurotrope joined the long list of Alzheimer's disease disappointments this week with the failure of Bryostatin-1 in a mid-stage trial, wiping 77% – $42m – from the company's market value. A look at cumulative market cap changes that can be attributed to news related to Alzheimer's projects shows that there has been a huge desertion of investor support for the field this year. *Vantage* constructed this analysis from *EvaluatePharma*'s EventAnalyzer, which tracks the biggest share price moves among global biopharma companies each day. An important caveat to bear in mind here is that sentiment that built or declined slowly will not have been captured here. However the chart clearly shows how major events have triggered the various ebbs and flows of optimism over the past decade, and those following the Alzheimer's field will not be surprised to see that this year is well into the red. Huge unmet need means that many investors will take positions in companies with skin in the game, for fear of missing out if the unexpected happens. But the field desperately needs to find a new way forward, as it is very hard to pinpoint projects that might prompt a recovery of the $39bn of market value that has eroded this year alone.

Cumulative industry market cap growth on Alzheimer's news

Source: EvaluatePharma

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World's first anti-aging trial gets green-light

Groundbreaking TAME trial, which directly targets aging as an endpoint, finally begins this November, reveals lead clinician Dr Nir Barzilai.

After closing the final $40m of its required $75m budget with a donation from a private source, the first drug trial directly targeting aging is set to begin at the end of this year, lead researcher Dr Nir Barzilai has revealed in an exclusive interview with Longevity.Technology.

Back in 2015, when his revolutionary anti-aging trial TAME finally received FDA approval, it would have been forgivable to think that Dr Barzilai had, at last, got past the hard part. But TAME went into financial limbo, with many wondering if it would ever be able to escape. "We wasted valuable time negotiating," said Dr Barzilai, director of the Institute for Aging Research at the Albert Einstein College of Medicine,"but we're finally on track." His trial TAME (Targeting Aging with Metformin) had been stalled for four years while he and his colleagues engaged in funding negotiations with the US NIH (National Institute of Health).

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Google claims to have reached quantum supremacy

Researchers say their quantum computer has calculated an impossible problem for ordinary machines

Madhumita Murgia and **Richard Waters** SEPTEMBER 20 2019

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Google claims to have built the first quantum computer that can carry out calculations beyond the ability of today's most powerful supercomputers, a landmark moment that has been hotly anticipated by researchers.

A paper by Google's researchers seen by the FT, that was briefly posted earlier this week on a Nasa website before being removed, claimed that their processor was able to perform a calculation in three minutes and 20 seconds that would take today's most advanced classical computer, known as Summit, approximately 10,000 years.

The researchers said this meant the "quantum supremacy", when quantum computers carry out calculations that had previously been impossible, had been achieved.

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Insilico Medicine Secures $37M in Series B Funding Led by Qiming Venture Partners

Alex Zhavoronkov, PhD Follow
Sep 10 · 3 min read

Original press release by Qiming Venture Partners

Tuesday, September 10, Hong Kong — Insilico Medicine, a pioneer in next-generation artificial intelligence technology for drug discovery, recently completes a $37 million funding round led by Qiming Venture Partners, joined by Eight Roads, F-Prime Capital, Lilly Asia Ventures, Sinovation Ventures, Baidu Ventures, Pavilion Capital, BOLD Capital Partners, Oculus co-founder, Michael Antonov, Longevity Vision Fund, Juvenescence and other investors including series A investors.

The Series B funding will be used to commercialize the validated generative chemistry and target identification technology. The company will also build up a senior management team with the experience in the pharmaceutical industry, further develop its pipeline in cancer, fibrosis, NASH, immunology, and CNS for the purposes of partnering with the pharmaceutical companies on specific therapeutic programs.

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World's first gene therapy for glycogen storage disease produces remarkable results

Consuming cornstarch every few hours has been the only available option for survival

Date: September 20, 2019

Source: University of Connecticut

Summary: The rare and deadly genetic liver disorder, GSD type Ia, affects children from infancy through adulthood, causing dangerously low blood sugar levels and constant dependence on glucose consumption in the form of cornstarch every few hours for survival. If a cornstarch dose is missed, the disease can lead to seizures and even death. A clinical trial originally set out to simply test the safety and dosage of the gene therapy for three patients with GSD Type Ia. The dramatic improvement in their lives was unexpected.

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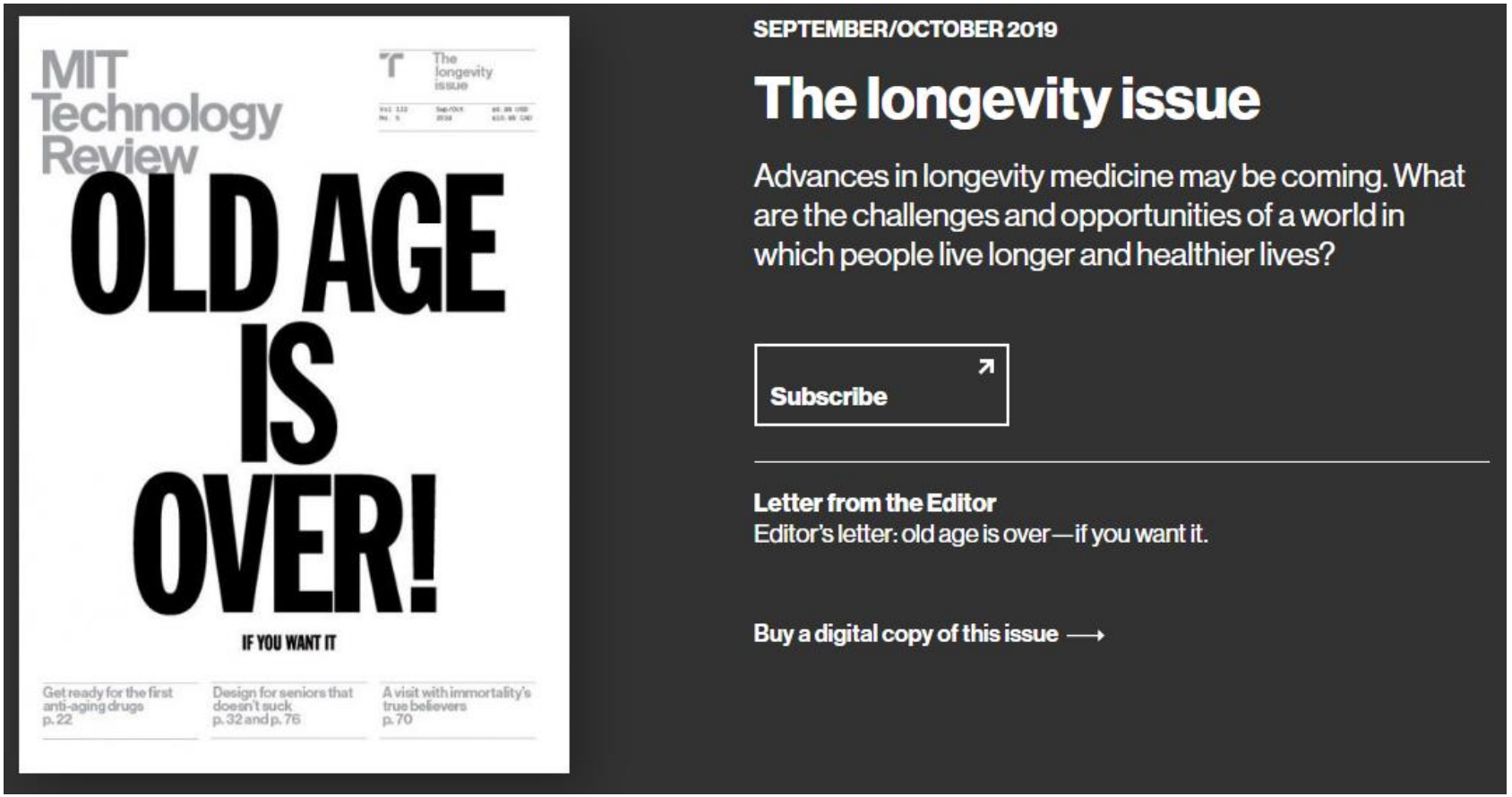
"I am clearly in favor of calling aging a disease," says Sven Bulterijs, cofounder of the Healthy Life Extension Society, a nonprofit organization in Brussels that considers aging a "universal human tragedy" with a root cause that can be found and tackled to make people live longer. "We don't say for cancer patients that it's insulting to call it a disease."



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Interferons: A molecular switch between damage and repair in ageing and Alzheimer's disease
N. Gorlé, R.E. Vandenbroucke
October 2019
Page 111148

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Multidimensional informatic deconvolution defines gender-specific roles of hypothalamic GIT2 in aging trajectories

In most species, females live longer than males. An understanding of this female longevity advantage will likely uncover novel anti-aging therapeutic targets. Here we investigated the transcriptomic responses in the hypothalamus – a key organ for somatic aging control – to the introduction of a simple aging-related molecular perturbation, *i.e.* GIT2 heterozygosity. Our previous work has demonstrated that GIT2 acts as a network controller of aging. A similar number of both total (1079-female, 1006-male) and gender-unique (577-female, 527-male) transcripts were significantly altered in response to GIT2 heterozygosity in early life-stage (2 month-old) mice. Despite a similar volume of transcriptomic disruption in females and males, a considerably stronger dataset coherency and functional annotation representation was observed for females. It was also evident that female mice possessed a greater resilience to pro-aging signaling pathways compared to males. Using a highly data-dependent natural language processing informatics pipeline, we identified novel functional data clusters that were connected by a coherent group of multifunctional transcripts. From these it was clear that females prioritized metabolic activity preservation compared to males to mitigate this pro-aging perturbation. These findings were corroborated by somatic metabolism analyses of living animals, demonstrating the efficacy of our new informatics pipeline.

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The real facts supporting Jeanne Calment as the oldest ever human FREE

Jean-Marie Robine, DED ✉, Michel Allard, MD, François R Herrmann, MD, MPH, Bernard Jeune, MD

The Journals of Gerontology: Series A, glz198, https://doi.org/10.1093/gerona/glz198
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Abstract

The 122 years and 165 days age claim of Jeanne Calment, the world oldest person who died in 1997, is the most thoroughly validated age claim. Recently the claim that families Calment and Billot organized a conspiracy concerning tax fraud based on identity fraud between mother and daughter gained international media attention. Here, we reference the original components of the validation as well as additional documentation to address various claims of the conspiracy theory and provide evidence for why these claims are based on inaccurate facts or unrelated to the death of Yvonne Billot-Calment, the daughter of Jeanne Calment, in 1934. Also, countering the contention that the occurrence of a 122 year old person is statistically impossible, mathematical models are presented which also supports the hypothesis that though extremely rare, as would be expected for the oldest person ever, Jeanne Calment's age claim is plausible. In total, the quality of the investigation supporting the claim of conspiracy as well as the mathematical analysis aiming to back it do not reach the level expected for a scientific publication.

EBioMedicine. 2019 Sep 6. pii: S2352-3964(19)30591-2. doi: 10.1016/j.ebiom.2019.08.069. [Epub ahead of print]

Senolytics decrease senescent cells in humans: Preliminary report from a clinical trial of Dasatinib plus Quercetin in individuals with diabetic kidney disease.

Abstract

BACKGROUND: Senescent cells, which can release factors that cause inflammation and dysfunction, the senescence-associated secretory phenotype (SASP), accumulate with ageing and at etiological sites in multiple chronic diseases. Senolytics, including the combination of Dasatinib and Quercetin (D + Q), selectively eliminate senescent cells by transiently disabling pro-survival networks that defend them against their own apoptotic environment. In the first clinical trial of senolytics, D + Q improved physical function in patients with idiopathic pulmonary fibrosis (IPF), a fatal senescence-associated disease, but to date, no peer-reviewed study has directly demonstrated that senolytics decrease senescent cells in humans.

METHODS: In an open label Phase 1 pilot study, we administered 3 days of oral D 100 mg and Q 1000 mg to subjects with diabetic kidney disease (N = 9; 68·7 ± 3·1 years old; 2 female; BMI:33·9 ± 2·3 kg/m^2; eGFR:27·0 ± 2·1 mL/min/1·73m^2). Adipose tissue, skin biopsies, and blood were collected before and 11 days after completing senolytic treatment. Senescent cell and macrophage/Langerhans cell markers and circulating SASP factors were assayed.

FINDINGS: D + Q reduced adipose tissue senescent cell burden within 11 days, with decreases in p16^{INK4A}-and p21^{CIP1}-expressing cells, cells with senescence-associated β-galactosidase activity, and adipocyte progenitors with limited replicative potential. Adipose tissue macrophages, which are attracted, anchored, and activated by senescent cells, and crown-like structures were decreased. Skin epidermal p16^{INK4A+} and p21^{CIP1+} cells were reduced, as were circulating SASP factors, including IL-1α, IL-6, and MMPs-9 and -12.

INTERPRETATION: "Hit-and-run" treatment with senolytics, which in the case of D + Q have elimination half-lives <11 h, significantly decreases senescent cell burden in humans. FUND: NIH and Foundations. ClinicalTrials.gov Identifier: NCT02848131. Senescence, Frailty, and Mesenchymal Stem Cell Functionality in Chronic Kidney Disease: Effect of Senolytic Agents.

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SILAC Analysis Reveals Increased Secretion of Hemostasis-Related Factors by Senescent Cells

Cellular senescence irreversibly arrests cell proliferation, accompanied by a multi-component senescence-associated secretory phenotype (SASP) that participates in several age-related diseases. Using stable isotope labeling with amino acids (SILACs) and cultured cells, we identify 343 SASP proteins that senescent human fibroblasts secrete at 2-fold or higher levels compared with quiescent cell counterparts. Bioinformatic analysis reveals that 44 of these proteins participate in hemostasis, a process not previously linked with cellular senescence. We validated the expression of some of these SASP factors in cultured cells and *in vivo*. Mice treated with the chemotherapeutic agent doxorubicin, which induces widespread cellular senescence *in vivo*, show increased blood clotting. Conversely, selective removal of senescent cells using transgenic p16-3MR mice showed that clearing senescent cells attenuates the increased clotting caused by doxorubicin. Our study provides an in-depth, unbiased analysis of the SASP and unveils a function for cellular senescence in hemostasis.

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Transient induction of telomerase expression mediates senescence and reduces tumorigenesis in primary fibroblasts

Telomerase is an enzymatic ribonucleoprotein complex that acts as a reverse transcriptase in the elongation of telomeres. Telomerase activity is well documented in embryonic stem cells and the vast majority of tumor cells, but its role in somatic cells remains to be understood. Here, we report an unexpected function of telomerase during cellular senescence and tumorigenesis. We crossed *Tert* heterozygous knockout mice ($mTert^{+/-}$) for 26 generations, during which time there was progressive shortening of telomeres, and obtained primary skin fibroblasts from $mTert^{+/+}$ and $mTert^{-/-}$ progeny of the 26th cross. As a consequence of insufficient telomerase activities in prior generations, both $mTert^{+/+}$ and $mTert^{-/-}$ fibroblasts showed comparable and extremely short telomere length. However, $mTert^{-/-}$ cells approached cellular senescence faster and exhibited a significantly higher rate of malignant transformation than $mTert^{+/+}$ cells. Furthermore, an evident up-regulation of telomerase reverse-transcriptase (TERT) expression was detected in $mTert^{+/+}$ cells at the presenescence stage. Moreover, removal or down-regulation of TERT expression in $mTert^{+/+}$ and human primary fibroblast cells via CRISPR/Cas9 or shRNA recapitulated $mTert^{-/-}$ phenotypes of accelerated senescence and transformation, and overexpression of TERT in $mTert^{-/-}$ cells rescued these phenotypes. Taking these data together, this study suggests that TERT has a previously underappreciated, protective role in buffering senescence stresses due to short, dysfunctional telomeres, and preventing malignant transformation.

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A human tissue-specific transcriptomic analysis reveals a complex relationship between aging, cancer, and cellular senescence

Kasit Chatsirisupachai, Daniel Palmer, Susana Ferreira, João Pedro de Magalhães

Aging is the biggest risk factor for cancer, but the mechanisms linking these two processes remain unclear. Using GTEx and TCGA data, we compared genes differentially expressed with age and genes differentially expressed in cancer among nine human tissues. In most tissues, aging and cancer gene expression pattern changed in the opposite direction. The exception was thyroid and uterus, where we found transcriptomic changes in the same direction in aging and in their corresponding cancers. The overlapping sets between genes differentially expressed with age and genes differentially expressed in cancer across tissues were enriched for several processes, mainly cell cycle and the immune system. Moreover, cellular senescence signatures, derived from a meta-analysis, changed in the same direction as aging in human tissues and in the opposite direction of cancer signatures. Therefore, transcriptomic changes in aging and in cellular senescence might relate to a decrease in cell proliferation, while cancer transcriptomic changes shift toward enhanced cell division. Our results highlight the complex relationship between aging and cancer and suggest that, while in general aging processes might be opposite to cancer, the transcriptomic links between human aging and cancer are tissue-specific.

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Restoration of Olfactory Memory in *Drosophila* Overexpressing Human Alzheimer's Disease Associated Tau by Manipulation of L-Type Ca^{2+} Channels

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The cellular underpinnings of memory deficits in Alzheimer's disease (AD) are poorly understood. We utilized the tractable neural circuits sub-serving memory in *Drosophila* to investigate the role of impaired Ca^{2+} handling in memory deficits caused by expression of human 0N4R isoform of tau which is associated with AD. Expression of tau in mushroom body neuropils, or a subset of mushroom body output neurons, led to impaired memory. By using the Ca^{2+} reporter GCaMP6f, we observed changes in Ca^{2+} signaling when tau was expressed in these neurons, an effect that could be blocked by the L-type Ca^{2+} channel antagonist nimodipine or reversed by *RNAi* knock-down of the L-type channel gene. The L-type Ca^{2+} channel itself is required for memory formation, however, *RNAi* knock-down of the L-type Ca^{2+} channel in neurons overexpressing human tau resulted in flies whose memory is restored to levels equivalent to wild-type. Expression data suggest that *Drosophila* L-type Ca^{2+} channel mRNA levels are increased upon tau expression in neurons, thus contributing to the effects observed on memory and intracellular Ca^{2+} homeostasis. Together, our Ca^{2+} imaging and memory experiments suggest that expression of the 0N4R isoform of human tau increases the number of L-type Ca^{2+} channels in the membrane resulting in changes in neuronal excitability that can be ameliorated by *RNAi* knockdown or pharmacological blockade of L-type Ca^{2+} channels. This highlights a role for L-type Ca^{2+} channels in tauopathy and their potential as a therapeutic target for AD.

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Sustained microglial depletion with CSF1R inhibitor impairs parenchymal plaque development in an Alzheimer's disease model

Many risk genes for the development of Alzheimer's disease (AD) are exclusively or highly expressed in myeloid cells. Microglia are dependent on colony-stimulating factor 1 receptor (CSF1R) signaling for their survival. We designed and synthesized a highly selective brain-penetrant CSF1R inhibitor (PLX5622) allowing for extended and specific microglial elimination, preceding and during pathology development. We find that in the 5xFAD mouse model of AD, plaques fail to form in the parenchymal space following microglial depletion, except in areas containing surviving microglia. Instead, Aβ deposits in cortical blood vessels reminiscent of cerebral amyloid angiopathy. Altered gene expression in the 5xFAD hippocampus is also reversed by the absence of microglia. Transcriptional analyses of the residual plaque-forming microglia show they exhibit a disease-associated microglia profile. Collectively, we describe the structure, formulation, and efficacy of PLX5622, which allows for sustained microglial depletion and identify roles of microglia in initiating plaque pathogenesis.

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A Breakdown in Metabolic Reprogramming Causes Microglia Dysfunction in Alzheimer's Disease

Reactive microglia are a major pathological feature of Alzheimer's disease (AD). However, the exact role of microglia in AD pathogenesis is still unclear. Here, using metabolic profiling, we found that exposure to amyloid-β triggers acute microglial inflammation accompanied by metabolic reprogramming from oxidative phosphorylation to glycolysis. It was dependent on the mTOR-HIF-1α pathway. However, once activated, microglia reached a chronic tolerant phase as a result of broad defects in energy metabolisms and subsequently diminished immune responses, including cytokine secretion and phagocytosis. Using genome-wide RNA sequencing and multiphoton microscopy techniques, we further identified metabolically defective microglia in 5XFAD mice, an AD mouse model. Finally, we showed that metabolic boosting with recombinant interferon-γ treatment reversed the defective glycolytic metabolism and inflammatory functions of microglia, thereby mitigating the AD pathology of 5XFAD mice. Collectively, metabolic reprogramming is crucial for microglial functions in AD, and modulating metabolism might be a new therapeutic strategy for AD.

PLoS One. 2019 Sep 23;14(9):e0222921. doi: 10.1371/journal.pone.0222921. eCollection 2019.

Computational identification of key genes that may regulate gene expression reprogramming in Alzheimer's patients.

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Abstract

The dementia epidemic is likely to expand worldwide as the aging population continues to grow. A better understanding of the molecular mechanisms that lead to dementia is expected to reveal potentially modifiable risk factors that could contribute to the development of prevention strategies. Alzheimer's disease is the most prevalent form of dementia. Currently we only partially understand some of the pathophysiological mechanisms that lead to development of the disease in aging individuals. In this study, Switch Miner software was used to identify key switch genes in the brain whose expression may lead to the development of Alzheimer's disease. The results indicate that switch genes are enriched in pathways involved in the proteasome, oxidative phosphorylation, Parkinson's disease, Huntington's disease, Alzheimer's disease and metabolism in the hippocampus and posterior cingulate cortex. Network analysis identified the krupel like factor 9 (KLF9), potassium channel tetramerization domain 2 (KCTD2), Sp1 transcription factor (SP1) and chromodomain helicase DNA binding protein 1 (CHD1) as key transcriptional regulators of switch genes in the brain of AD patients. These transcriptions factors have been implicated in conditions associated with Alzheimer's disease, including diabetes, glucocorticoid signaling, stroke, and sleep disorders. The specific pathways affected reveal potential modifiable risk factors by lifestyle changes.

Aging (Albany NY). 2019 Sep 14;11. doi: 10.18632/aging.102273. [Epub ahead of print]

Attenuated activation of the unfolded protein response following exercise in skeletal muscle of older adults.

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Abstract

Sarcopenia is linked with impaired adaptive responses to exercise in aging skeletal muscle. The unfolded protein response (UPR) is an important intramyocellular molecular response pathway that is activated by exercise. The influence of age on skeletal muscle adaptive UPR in response to exercise, and the relationship to other key exercise-responsive regulatory pathways is not well-understood. We evaluated age-related changes in transcriptional markers of UPR activation following a single bout of resistance exercise in 12 young (27 ± 5yrs) and 12 older (75 ± 5yrs) healthy men and women. At baseline, there were modest differences in expression of UPR-related genes in young and older adults. Following exercise, transcriptional markers of UPR pathway activation were attenuated in older adults compared to young based on specific salient UPR-related genes and gene set enrichment analysis. The coordination of post-exercise transcriptional patterns between the UPR pathway, p53/p21 axis of autophagy, and satellite cell differentiation were less evident in older compared to young adults. In conclusion, transcriptomic analysis revealed an age-related decline in the adaptive UPR transcriptional response following a single bout of exercise that could contribute to impaired exercise responsiveness with age.

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Exp Gerontol. 2019 Sep 12:110736. doi: 10.1016/j.exger.2019.110736. [Epub ahead of print]

Dietary restriction in ILSXISS mice is associated with widespread changes in splicing regulatory factor expression levels.

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Abstract

Dietary restriction (DR) represents one of the most reproducible interventions to extend lifespan and improve health outcomes in a wide range of species, but substantial variability in DR response has been observed, both between and within species. The mechanisms underlying this variation in effect are still not well characterised. Splicing regulatory factors have been implicated in the pathways linked with DR-induced longevity in C. elegans and are associated with lifespan itself in mice and humans. We used qRT-PCR to measure the expression levels of a panel of 20 age- and lifespan-associated splicing regulatory factors in brain, heart and kidney derived from three recombinant inbred strains of mice with variable lifespan responses to short-term (2 months) or long-term (10 months) 40% DR to determine their relationship to DR-induced longevity. We identified 3 patterns of association; i) splicing factors associated with DR alone, ii) splicing factors associated with strain alone or iii) splicing factors associated with both DR and strain. Tissue specific variation was noted in response to short term or long-term DR, with the majority of effects noted in brain following long term DR in the positive responder strain TejJ89. Association in heart and kidney were less evident, and occurred following short term DR. Splicing factors associated with both DR and strain may be mechanistically involved in strain-specific differences in response to DR. We provide here evidence concordant with a role for some splicing factors in the lifespan modulatory effects of DR across different mouse strains and in different tissues.

Cell Rep. 2019 Sep 10;28(11):2767-2776.e5. doi: 10.1016/j.celrep.2019.08.013.

αKlotho Regulates Age-Associated Vascular Calcification and Lifespan in Zebrafish.

Singh AP[1], Sosa MX[1], Fang J[1], Shanmukhappa SK[2], Hubaud A[1], Fawcett CH[1], Molind GJ[1], Tsai T[1], Capodieci P[3], Wetzel K[3], Sanchez E[1], Wang G[1], Coble M[1], Tang W[1], Cadena SM[4], Fishman MC[5], Glass DJ[6].

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Abstract

The hormone αKlotho regulates lifespan in mice, as knockouts die early of what appears to be accelerated aging due to hyperphosphatemia and soft tissue calcification. In contrast, the overexpression of αKlotho increases lifespan. Given the severe mouse phenotype, we generated zebrafish mutants for αklotho as well as its binding partner fibroblast growth factor-23 (fgf23). Both mutations cause shortened lifespan in zebrafish, with abrupt onset of behavioral and degenerative physical changes at around 5 months of age. There is a calcification of vessels throughout the body, most dramatically in the outflow tract of the heart, the bulbus arteriosus (BA). This calcification is associated with an ectopic activation of osteoclast differentiation pathways. These findings suggest that the gradual loss of αKlotho found in normal aging might give rise to ectopic calcification.

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Comp Biochem Physiol B Biochem Mol Biol. 2019 Sep 13:110352. doi: 10.1016/j.cbpb.2019.110352. [Epub ahead of print]

Comparative proteomic analysis of senescence in the freshwater cladoceran Daphnia pulex.

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Abstract

Cladocera are small freshwater crustaceans that have attracted considerable attention in recent years. They are commonly used for studying senescence. In this study, we used LC-MS/MS with eight-plex iTRAQ to perform a comparative proteomic analysis of senescence in Daphnia pulex. Of 3076 primordial proteins, 2325 were credible (the remaining were low-confidence proteins) and 247 significantly differentially expressed proteins (DEPs). Of the latter, 87, 91, and 69 DEPs were identified in the Day 15 vs. Day 5, Day 20 vs. Day 5, and Day 25 vs. Day 5 groups, respectively. Gene ontology enrichment analysis showed that oxidative damage may be the main cause of senescence in D. pulex. Using Kyoto Encyclopedia of Genes and Genomes pathway analysis, we found that the peroxisome pathway played an important role in aging. Our results suggest that D. pulex alleviates excessive oxidative damage by altering key enzymes involved in carbohydrate and protein metabolism.

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Single-cell transcriptomic profiling of the aging mouse brain

The mammalian brain is complex, with multiple cell types performing a variety of diverse functions, but exactly how each cell type is affected in aging remains largely unknown. Here we performed a single-cell transcriptomic analysis of young and old mouse brains. We provide comprehensive datasets of aging-related genes, pathways and ligand–receptor interactions in nearly all brain cell types. Our analysis identified gene signatures that vary in a coordinated manner across cell types and gene sets that are regulated in a cell-type specific manner, even at times in opposite directions. These data reveal that aging, rather than inducing a universal program, drives a distinct transcriptional course in each cell population, and they highlight key molecular processes, including ribosome biogenesis, underlying brain aging. Overall, these large-scale datasets (accessible online at https://portals.broadinstitute.org/single_cell/study/aging-mouse-brain) provide a resource for the neuroscience community that will facilitate additional discoveries directed towards understanding and modifying the aging process.

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Transcriptome analysis reveals the difference between "healthy" and "common" aging and their connection with age-related diseases

Lu Zeng, Jialiang Yang, Shouneng Peng, Jun Zhu, Bin Zhang, Yousin Suh, Zhidong Tu

A key goal of aging research is to understand mechanisms underlying healthy aging and use them to develop methods to promote the human healthspan. One approach is to identify gene regulations differentiating healthy aging from aging in the general population (i.e., "common" aging). In this study, we leveraged GTEx (Genotype-Tissue Expression) project data to investigate "healthy" and "common" aging in humans and their interconnection with diseases.

We selected GTEx donors who were not annotated with diseases to approximate a "healthy" aging cohort. We then compared the age-associated genes derived from this cohort with age-associated genes from our "common" aging cohort which included all GTEx donors; we also compared the "healthy" and "common" aging gene expressions with various disease-associated gene expression to elucidate the relationships among "healthy", "common" aging and disease. Our analyses showed that 1. "healthy" and "common" aging shared a large number of gene regulations; 2. Despite the substantial commonality, "healthy" and "common" aging genes also showed distinct function enrichment, and "common" aging genes had a higher enrichment for disease genes; 3. Disease-associated gene regulations were overall different from aging gene regulations. However, for genes regulated by both, their regulation directions were largely consistent, implying some aging processes could increase the susceptibility to disease development; and 4. Possible protective mechanisms were associated with the "healthy" aging gene regulations.

In summary, our work highlights several unique features of human "healthy" aging program. This new knowledge can be used for the development of therapeutics to promote human healthspan.

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Senescence in immunity against helminth parasites predicts adult mortality in a wild mammal

Our understanding of the deterioration in immune function in old age—immunosenescence—derives principally from studies of modern human populations and laboratory animals. The generality and significance of this process for systems experiencing complex, natural infections and environmental challenges are unknown. Here, we show that late-life declines in an important immune marker of resistance to helminth parasites in wild Soay sheep predict overwinter mortality. We found senescence in circulating antibody levels against a highly prevalent nematode worm, which was associated with reduced adult survival probability, independent of changes in body weight. These findings establish a role for immunosenescence in the ecology and evolution of natural populations.

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Reversal of epigenetic aging and immunosenescent trends in humans

Gregory M. Fahy, Robert T. Brooke, James P. Watson, Zinaida Good, Shreyas S. Vasanawala, Holden Maecker, Michael D. Leipold, David T. S. Lin, Michael S. Kobor, Steve Horvath

Epigenetic "clocks" can now surpass chronological age in accuracy for estimating biological age. Here, we use four such age estimators to show that epigenetic aging can be reversed in humans. Using a protocol intended to regenerate the thymus, we observed protective immunological changes, improved risk indices for many age-related diseases, and a mean epigenetic age approximately 1.5 years less than baseline after 1 year of treatment (−2.5-year change compared to no treatment at the end of the study). The rate of epigenetic aging reversal relative to chronological age accelerated from −1.6 year/year from 0–9 month to −6.5 year/year from 9–12 month. The GrimAge predictor of human morbidity and mortality showed a 2-year decrease in epigenetic vs. chronological age that persisted six months after discontinuing treatment. This is to our knowledge the first report of an increase, based on an epigenetic age estimator, in predicted human lifespan by means of a currently accessible aging intervention.

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An excreted small molecule promotes *C. elegans* reproductive development and aging

Excreted small-molecule signals can bias developmental trajectories and physiology in diverse animal species. However, the chemical identity of these signals remains largely obscure. Here we report identification of an unusual N-acylated glutamine derivative, nacq#1, that accelerates reproductive development and shortens lifespan in *Caenorhabditis elegans*. Produced predominantly by *C. elegans* males, nacq#1 hastens onset of sexual maturity in hermaphrodites by promoting exit from the larval dauer diapause and by accelerating late larval development. Even at picomolar concentrations, nacq#1 shortens hermaphrodite lifespan, suggesting a trade-off between reproductive investment and longevity. Acceleration of development by nacq#1 requires chemosensation and is dependent on three homologs of vertebrate steroid hormone receptors. Unlike ascaroside pheromones, which are restricted to nematodes, fatty acylated amino acid derivatives similar to nacq#1 have been reported from humans and invertebrates, suggesting that related compounds may serve signaling functions throughout metazoa.

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Mitochondrial bioenergetic changes during development as an indicator of C. elegans health-span.

Maglioni S, et al. Aging (Albany NY). 2019.
Show full citation

Abstract

Mild suppression of mitochondrial activity has beneficial effects across species. The nematode Caenorhabditis elegans is a versatile, genetically tractable model organism widely employed for aging studies, which has led to the identification of many of the known evolutionarily conserved mechanisms regulating lifespan. In C. elegans the pro-longevity effect of reducing mitochondrial function, for example by RNA interference, is only achieved if mitochondrial stress is applied during larval development. Surprisingly, a careful analysis of changes in mitochondrial functions resulting from such treatments during the developmental windows in which pro-longevity signals are programmed has never been carried out. Thus, although the powerful C. elegans genetics have led to the identification of different molecular mechanisms causally involved in mitochondrial stress control of longevity, specific functional mitochondrial biomarkers indicative or predictive of lifespan remain to be identified. To fill this gap, we systematically characterized multiple mitochondrial functional parameters at an early developmental stage in animals that are long-lived due to mild knockdown of twelve different mitochondrial proteins and correlated these parameters with animals' lifespan. We found that basal oxygen consumption rate and ATP-linked respiration positively correlate with lifespan extension and propose the testable hypothesis that the Bioenergetic Health Index can be used as a proxy to predict health-span outcomes.

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Sugar-derived AGEs accelerate pharyngeal pumping rate and increase the lifespan of Caenorhabditis elegans.

Papaevgeniou N, et al. Free Radic Res. 2019.
Show full citation

Abstract

All living organisms are normally undergoing aging. Dietary habits constitute the main environmental factor that may accelerate or decelerate this process. Advanced glycation end products (AGEs) are constituents of dietary products that are consumed daily, such as bread and milk. Although AGEs have been widely regarded as toxic agents, recent studies seem to contradict this view: they either find no adverse effects of AGEs or even attribute beneficial properties to them. The aim of our study was to investigate the effects of sugar-derived AGEs on organismal lifespan using as a model the nematode Caenorhabditis elegans. Exposure to sugar-derived AGEs prolonged the lifespan of wild type animals; this lifespan extension was accompanied by an enhanced pharyngeal pumping rate. We demonstrate that elevation of the pharyngeal pumping rate depends on W06A7.4 and eat-4 expression, as well as on daf-16, which encodes a FOXO family transcription factor. Our results suggest that sugar-derived AGEs modulate the lifespan of C. elegans at least in part through transcriptional regulation of pharyngeal pumping throughout the animals' lifespan.

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Melanoidins from Coffee, Cocoa, and Bread Are Able to Scavenge α-Dicarbonyl Compounds under Simulated Physiological Conditions

Hao Zhang, Hui Zhang, Antonio Dario Troise and Vincenzo Fogliano*

Free amino residues react with α-dicarbonyl compounds (DCs) contributing to the formation of advanced glycation end products (AGEs). Phenolic compounds can scavenge DCs, thus controlling the dietary carbonyl load. This study showed that high-molecular weight cocoa melanoidins (HMW-COM), HMW bread melanoidins (HMW-BM), and especially HMW coffee melanoidins (HMW-CM) are effective DC scavengers. HMW-CM (1 mg/mL) scavenged more than 40% DCs within 2 h under simulated physiological conditions, suggesting some physiological relevance. Partial acid hydrolysis of HMW-CM decreased the dicarbonyl trapping capacity, demonstrating that the ability to react with glyoxal, methylglyoxal (MGO), and diacetyl was mainly because of polyphenols bound to macromolecules. Caffeic acid (CA) and 3-caffeoylquinic acid showed a DC-scavenging kinetic profile similar to that of HMW-CM, while mass spectrometry data confirmed that hydroxyalkylation and aromatic substitution reactions led to the formation of a stable adduct between CA and MGO. These findings corroborated the idea that antioxidant-rich indigestible materials could limit carbonyl stress and AGE formation across the gastrointestinal tract.

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Glucosepane is associated with changes to structural and physical properties of collagen fibrils

Collagen glycation, and in particular the formation of advanced glycation end-product (AGE) crosslinks, plays a central role in the ageing process and in many of the long-term complications of diabetes. Glucosepane, the most abundant and relevant AGE crosslink, has been suggested to increase the stiffness of tissue and reduce its solubility, although no evidence is available concerning the mechanisms. We have used a combination of computational and experimental techniques to study a collagen-rich tissue with a relatively simple organisation to further our understanding of the impact of glucosepane on the structural and physical properties of collagen fibrils. Our work shows that glucosepane levels increase dramatically in aged tendon tissue and are associated with the reduced density of collagen packing and increased porosity to water molecules. Our studies provide the basis to understand many of the tissue dysfunctions associated with ageing and diabetes across a range of different tissues types.

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Variation in actuarial senescence does not reflect life span variation across mammals

Guillaume Péron, Jean-François Lemaître, Victor Ronget, Morgane Tidière, Jean-Michel Gaillard

Version 2 ▾ Published: September 13, 2019 • https://doi.org/10.1371/journal.pbio.3000432

Abstract

The concept of actuarial senescence (defined here as the increase in mortality hazards with age) is often confounded with life span duration, which obscures the relative role of age-dependent and age-independent processes in shaping the variation in life span. We use the opportunity afforded by the Species360 database, a collection of individual life span records in captivity, to analyze age-specific mortality patterns in relation to variation in life span. We report evidence of actuarial senescence across 96 mammal species. We identify the life stage (juvenile, prime-age, or senescent) that contributes the most to the observed variation in life span across species. Actuarial senescence only accounted for 35%–50% of the variance in life span across species, depending on the body mass category. We computed the sensitivity and elasticity of life span to five parameters that represent the three stages of the age-specific mortality curve—namely, the duration of the juvenile stage, the mean juvenile mortality, the prime-age (i.e., minimum) adult mortality, the age at the onset of actuarial senescence, and the rate of actuarial senescence. Next, we computed the between-species variance in these five parameters. Combining the two steps, we computed the relative contribution of each of the five parameters to the variance in life span across species. Variation in life span was increasingly driven by the intensity of actuarial senescence and decreasingly driven by prime-age adult mortality from small to large species because of changes in the elasticity of life span to these parameters, even if all the adult survival parameters consistently exhibited a canalization pattern of weaker variability among long-lived species than among short-lived ones. Our work unambiguously demonstrates that life span cannot be used to measure the strength of actuarial senescence, because a substantial and variable proportion of life span variation across mammals is not related to actuarial senescence metrics.

REVIEWS/COMMENTS/ METHODS/EDITORIALS

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REGENERATIVE MEDICINE, VOL. 14, NO. 9 | REVIEW

Open Access

Toward a unified theory of aging and regeneration

Michael D West, Hal Sternberg, Ivan Labat, Jeffrey Janus, Karen B Chapman, Nafees N Malik, Aubrey DNJ de Grey & Dana Larocca

Published Online: 28 Aug 2019 | https://doi.org/10.2217/rme-2019-0062

Growing evidence supports the antagonistic pleiotropy theory of mammalian aging. Accordingly, changes in gene expression following the pluripotency transition, and subsequent transitions such as the embryonic–fetal transition, while providing tumor suppressive and antiviral survival benefits also result in a loss of regenerative potential leading to age-related fibrosis and degenerative diseases. However, reprogramming somatic cells to pluripotency demonstrates the possibility of restoring telomerase and embryonic regeneration pathways and thus reversing the age-related decline in regenerative capacity. A unified model of aging and loss of regenerative potential is emerging that may ultimately be translated into new therapeutic approaches for establishing induced tissue regeneration and modulation of the embryo-onco phenotype of cancer.

Arrhythmogenic foods – A growing medical problem

Arrhythmogenic ingredients in our diet such as mushrooms, licorice, toxic honey, liquid protein drinks, etc. have long been recognized as rare but important considerations in the differential diagnosis of arrhythmias. Anecdotal reports of torsades de pointes (TdP), arrhythmias and/or sudden death and small studies in normal subjects have suggested that simple ingredients such as grapefruit juice or ingredients in energy drinks marketed as dietary supplements could have direct arrhythmogenic actions, especially in patients with congenital long QT syndrome (cLQTS). Two recent studies that employed the industry-standard "thorough QT" trial design leave no doubt that grapefruit juice and some energy drinks can prolong the QTc interval and to exceed 500 msec. in some patients with cLQTS, a threshold known to signal imminent danger. These reports raise numerous clinically important questions such as which other patients may be at risk of arrhythmias. For example, patients with multiple clinical risk factors for TdP (hypokalemia, bradycardia, female sex, etc.) may be at risk from these and possibly other dietary ingredients ingested by millions of people each day. It is essential that further research evaluate the safety of these and similar food products and that vulnerable patients, especially those with cLQTS, be warned of this serious and emerging threat.

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Alzheimer Disease: An Update on Pathobiology and Treatment Strategies

Justin M. Long [1], David M. Holtzman [1]

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https://doi.org/10.1016/j.cell.2019.09.001

Alzheimer disease (AD) is a heterogeneous disease with a complex pathobiology. The presence of extracellular β-amyloid deposition as neuritic plaques and intracellular accumulation of hyperphosphorylated tau as neurofibrillary tangles remains the primary neuropathologic criteria for AD diagnosis. However, a number of recent fundamental discoveries highlight important pathological roles for other critical cellular and molecular processes. Despite this, no disease-modifying treatment currently exists, and numerous phase 3 clinical trials have failed to demonstrate benefits. Here, we review recent advances in our understanding of AD pathobiology and discuss current treatment strategies, highlighting recent clinical trials and opportunities for developing future disease-modifying therapies.

Gerontology. 2019 Sep 13:1-10. doi: 10.1159/000502257. [Epub ahead of print]

Metformin and Aging: A Review.

Glossmann HH[1], Lutz OMD[2].

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2 Austrian Drug Screening Institute GmbH, Innsbruck, Austria.

Abstract

Metformin is sometimes proposed to be an "anti-aging" drug, based on preclinical experiments with lower-order organisms and numerous retrospective data on beneficial health outcomes for type 2 diabetics. Large prospective, placebo-controlled trials are planned, in pilot stage or running, to find a new use (or indication) for an aging population. As one of the metformin trials has "frailty" as its endpoint, similar to a trial with a plant-derived senolytic, the latter class of novel anti-aging drugs is briefly discussed. Concerns exist not only for vitamin B12 and B6 deficiencies, but also about whether there are adverse effects of metformin on individuals who try to remain healthy by maintaining cardiovascular fitness via exercise.

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Intern Emerg Med. 2019 Sep 21. doi: 10.1007/s11739-019-02191-4. [Epub ahead of print]

Aspirin in primary prevention: the triumph of clinical judgement over complex equations.

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Abstract

Aspirin, in 2017, has celebrated its 120th birthday. The efficacy and safety of low-dose aspirin in secondary prevention of cardiovascular disease is well supported by many studies, instead in primary prevention it remains controversial, especially in the aftermath of the publication in 2018 of three novel primary prevention randomized clinical trials, showing that the benefit of low-dose aspirin, although additive to that of statin, is counterbalanced by an excess of (mainly gastrointestinal) bleeding events. The signal for a net benefit seems to be even more controversial in the elderly starting aspirin after the age of 70 years. While international guidelines have promptly downgraded their recommendations to more conservative indications, the practicing clinician is called to make the effort to individualize the treatment, after careful evaluation of the haemorrhagic risk vis-a-vis the risk to develop, in the mid-term and long-term follow-up, major cardiovascular events or cancer. This is a particularly complex task, given the different immediate and long-term impact of diverse outcomes on health, the dynamic nature over time of the benefit/risk balance, prompting periodic re-assessments of its indication, and the interindividual variability in aspirin response. The chemopreventive properties of aspirin, anticipated by a large body of epidemiological and mechanistic evidence, are awaiting their final confirmation by the long-term follow-up of the latest trials specifically designed to assess this endpoint, with the expectation to subvert the delicate benefit/risk balance of aspirin in primary prevention. This review is intended to provide an interpretation of past and current evidence to guide clinical decision making on the contemporary patient.

Aging Cell. 2019 Sep 27:e13048. doi: 10.1111/acel.13048. [Epub ahead of print]

The role of lipid metabolism in aging, lifespan regulation, and age-related disease.

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Abstract

An emerging body of data suggests that lipid metabolism has an important role to play in the aging process. Indeed, a plethora of dietary, pharmacological, genetic, and surgical lipid-related interventions extend lifespan in nematodes, fruit flies, mice, and rats. For example, the impairment of genes involved in ceramide and sphingolipid synthesis extends lifespan in both worms and flies. The overexpression of fatty acid amide hydrolase or lysosomal lipase prolongs life in Caenorhabditis elegans, while the overexpression of diacylglycerol lipase enhances longevity in both C. elegans and Drosophila melanogaster. The surgical removal of adipose tissue extends lifespan in rats, and increased expression of apolipoprotein D enhances survival in both flies and mice. Mouse lifespan can be additionally extended by the genetic deletion of diacylglycerol acyltransferase 1, treatment with the steroid 17-α-estradiol, or a ketogenic diet. Moreover, deletion of the phospholipase A2 receptor improves various healthspan parameters in a progeria mouse model. Genome-wide association studies have found several lipid-related variants to be associated with human aging. For example, the epsilon 2 and epsilon 4 alleles of apolipoprotein E are associated with extreme longevity and late-onset neurodegenerative disease, respectively. In humans, blood triglyceride levels tend to increase, while blood lysophosphatidylcholine levels tend to decrease with age. Specific sphingolipid and phospholipid blood profiles have also been shown to change with age and are associated with exceptional human longevity. These data suggest that lipid-related interventions may improve human healthspan and that blood lipids likely represent a rich source of human aging biomarkers.

Nat Rev Microbiol. 2019 Sep 18. doi: 10.1038/s41579-019-0253-y. [Epub ahead of print]

Microbial ageing and longevity.

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Erratum in

Publisher Correction: Microbial ageing and longevity. [Nat Rev Microbiol. 2019]

Abstract

Longevity reflects the ability to maintain homeostatic conditions necessary for life as an organism ages. A long-lived organism must contend not only with environmental hazards but also with internal entropy and macromolecular damage that result in the loss of fitness during ageing, a phenomenon known as senescence. Although central to many of the core concepts in biology, ageing and longevity have primarily been investigated in sexually reproducing, multicellular organisms. However, growing evidence suggests that microorganisms undergo senescence, and can also exhibit extreme longevity. In this Review, we integrate theoretical and empirical insights to establish a unified perspective on senescence and longevity. We discuss the evolutionary origins, genetic mechanisms and functional consequences of microbial ageing. In addition to having biomedical implications, insights into microbial ageing shed light on the role of ageing in the origin of life and the upper limits to longevity.

Front Cell Dev Biol. 2019 Sep 6;7:183. doi: 10.3389/fcell.2019.00183. eCollection 2019.

Maximizing Longevity and Healthspan: Multiple Approaches All Converging on Autophagy.

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Abstract

Our understanding of the molecular basis of aging has greatly increased over the past few decades. In this review, we provide an overview of the key signaling pathways associated with aging, and whose modulation has been shown to extend lifespan in a range of model organisms. We also describe how these pathways converge onto autophagy, a catabolic process that functions to recycle dysfunctional cellular material and maintains energy homeostasis. Finally, we consider various approaches of therapeutically modulating these longevity pathways, highlighting exercise as a potent geroprotector.

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Mitochondria in the signaling pathways that control longevity and health span

Mansour Akbari [a], Thomas B.L. Kirkwood [a, b], Vilhelm A. Bohr [a, c]

Genetic and pharmacological intervention studies have identified evolutionarily conserved and functionally interconnected networks of cellular energy homeostasis, nutrient-sensing, and genome damage response signaling pathways, as prominent regulators of longevity and health span in various species. Mitochondria are the primary sites of ATP production and are key players in several other important cellular processes. Mitochondrial dysfunction diminishes tissue and organ functional performance and is a commonly considered feature of the aging process. Here we review the evidence that through reciprocal and multilevel functional interactions, mitochondria are implicated in the lifespan modulation function of these pathways, which altogether constitute a highly dynamic and complex system that controls the aging process. An important characteristic of these pathways is their extensive crosstalk and apparent malleability to modification by non-invasive pharmacological, dietary, and lifestyle interventions, with promising effects on lifespan and health span in animal models and potentially also in humans.

Physiol Rev. 2019 Sep 20. doi: 10.1152/physrev.00001.2019. [Epub ahead of print]

Methylglyoxal, a highly reactive dicarbonyl compound, in diabetes, its vascular complications and other age-related diseases.

Schalkwijk C[1], Stehouwer CD[2].

Author information

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Abstract

The formation and accumulation of methylglyoxal (MGO), a highly reactive dicarbonyl compound, has been implicated in the pathogenesis of type 2 diabetes, vascular complications of diabetes, and several other age-related chronic inflammatory diseases such as cardiovascular disease, cancer and disorders of the central nervous system. MGO is mainly formed as a byproduct of glycolysis and, under physiological circumstances, detoxified by the glyoxalase system. MGO is the major precursor of non-enzymatic glycation of proteins and DNA, subsequently leading to the formation of advanced glycation endproducts (AGEs). MGO and MGO-derived AGEs can impact on organs and tissues affecting their functions and structure. This review summarizes the mechanisms through which MGO is formed, its detoxification by the glyoxalase system, and its effect on biochemical pathways in relation to the development of diabetes, vascular complications of diabetes and other age-related diseases. Although therapies to treat MGO-associated complications are not yet available for application in clinical practice, several strategies to lower MGO have been developed over the years. We will summarize several new directions to target MGO stress including glyoxalase inducers and MGO scavengers. Diminishing MGO burden can potentially form the basis for new treatment strategies for age-related disorders in which MGO plays a pivotal role.

OTHER RESEARCH

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Deep learning enables rapid identification of potent DDR1 kinase inhibitors

Alex Zhavoronkov ✉, Yan A. Ivanenkov, Alex Aliper, Mark S. Veselov, Vladimir A. Aladinskiy, Anastasiya V. Aladinskaya, Victor A. Terentiev, Daniil A. Polykovskiy, Maksim D. Kuznetsov, Arip Asadulaev, Yury Volkov, Artem Zholus, Rim R. Shayakhmetov, Alexander Zhebrak, Lidiya I. Minaeva, Bogdan A. Zagribelnyy, Lennart H. Lee, Richard Soll, David Madge, Li Xing, Tao Guo & Alán Aspuru-Guzik

We have developed a deep generative model, generative tensorial reinforcement learning (GENTRL), for de novo small-molecule design. GENTRL optimizes synthetic feasibility, novelty, and biological activity. We used GENTRL to discover potent inhibitors of discoidin domain receptor 1 (DDR1), a kinase target implicated in fibrosis and other diseases, in 21 days. Four compounds were active in biochemical assays, and two were validated in cell-based assays. One lead candidate was tested and demonstrated favorable pharmacokinetics in mice.

Ultrasound imaging of gene expression in mammalian cells

Sounding out mammalian cells

Live cell imaging allows us to observe cellular processes in real time. Most methods rely on light, and the poor penetration of light into tissues limits their application. Ultrasound penetrates tissues, and cellular reporters that respond to ultrasound have been developed recently. These reporters are air-filled protein structures that provide buoyancy in the bacteria they are derived from, but when surrounded by a fluid medium, they reflect sound waves. Farhadi *et al.* achieved expression from multiple genes to create these complex structures in mammalian cells. In addition to optimizing reporter production and detection, they visualize cells in a proof-of-principle experiment in mouse tumor xenografts.

Science, this issue p. **1469**

Abstract

The study of cellular processes occurring inside intact organisms requires methods to visualize cellular functions such as gene expression in deep tissues. Ultrasound is a widely used biomedical technology enabling noninvasive imaging with high spatial and temporal resolution. However, no genetically encoded molecular reporters are available to connect ultrasound contrast to gene expression in mammalian cells. To address this limitation, we introduce mammalian acoustic reporter genes. Starting with a gene cluster derived from bacteria, we engineered a eukaryotic genetic program whose introduction into mammalian cells results in the expression of intracellular air-filled protein nanostructures called gas vesicles, which produce ultrasound contrast. Mammalian acoustic reporter genes allow cells to be visualized at volumetric densities below 0.5% and permit high-resolution imaging of gene expression in living animals.

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Real-time volumetric microscopy of in vivo dynamics and large-scale samples with SCAPE 2.0

The limited per-pixel bandwidth of most microscopy methods requires compromises between field of view, sampling density and imaging speed. This limitation constrains studies involving complex motion or fast cellular signaling, and presents a major bottleneck for high-throughput structural imaging. Here, we combine high-speed intensified camera technology with a versatile, reconfigurable and dramatically improved Swept, Confocally Aligned Planar Excitation (SCAPE) microscope design that can achieve high-resolution volumetric imaging at over 300 volumes per second and over 1.2 GHz pixel rates. We demonstrate near-isotropic sampling in freely moving *Caenorhabditis elegans*, and analyze real-time blood flow and calcium dynamics in the beating zebrafish heart. The same system also permits high-throughput structural imaging of mounted, intact, cleared and expanded samples. SCAPE 2.0's significantly lower photodamage compared to point-scanning techniques is also confirmed. Our results demonstrate that SCAPE 2.0 is a powerful, yet accessible imaging platform for myriad emerging high-speed dynamic and high-throughput volumetric microscopy applications.

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Off-target toxicity is a common mechanism of action of cancer drugs undergoing clinical trials

Ann Lin[1,2,*], Christopher J. Giuliano[1,2,*], Ann Palladino[1], Kristen M. John[1,3], Connor Abramowicz[1,4], Monet Lou Yuan[1,5], Erin...

Abstract

Ninety-seven percent of drug-indication pairs that are tested in clinical trials in oncology never advance to receive U.S. Food and Drug Administration approval. While lack of efficacy and dose-limiting toxicities are the most common causes of trial failure, the reason(s) why so many new drugs encounter these problems is not well understood. Using CRISPR-Cas9 mutagenesis, we investigated a set of cancer drugs and drug targets in various stages of clinical testing. We show that—contrary to previous reports obtained predominantly with RNA interference and small-molecule inhibitors—the proteins ostensibly targeted by these drugs are nonessential for cancer cell proliferation. Moreover, the efficacy of each drug that we tested was unaffected by the loss of its putative target, indicating that these compounds kill cells via off-target effects. By applying a genetic target-deconvolution strategy, we found that the mischaracterized anticancer agent OTS964 is actually a potent inhibitor of the cyclin-dependent kinase CDK11 and that multiple cancer types are addicted to CDK11 expression. We suggest that stringent genetic validation of the mechanism of action of cancer drugs in the preclinical setting may decrease the number of therapies tested in human patients that fail to provide any clinical benefit.

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Fatty Acid Metabolites Combine with Reduced β Oxidation to Activate Th17 Inflammation in Human Type 2 Diabetes

Mechanisms that regulate metabolites and downstream energy generation are key determinants of T cell cytokine production, but the processes underlying the Th17 profile that predicts the metabolic status of people with obesity are untested. Th17 function requires fatty acid uptake, and our new data show that blockade of CPT1A inhibits Th17-associated cytokine production by cells from people with type 2 diabetes (T2D). A low CACT:CPT1A ratio in immune cells from T2D subjects indicates altered mitochondrial function and coincides with the preference of these cells to generate ATP through glycolysis rather than fatty acid oxidation. However, glycolysis was not critical for Th17 cytokines. Instead, β oxidation blockade or CACT knockdown in T cells from lean subjects to mimic characteristics of T2D causes cells to utilize ^{16}C-fatty acylcarnitine to support Th17 cytokines. These data show long-chain acylcarnitine combines with compromised β oxidation to promote disease-predictive inflammation in human T2D.