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Sven Bulterijs

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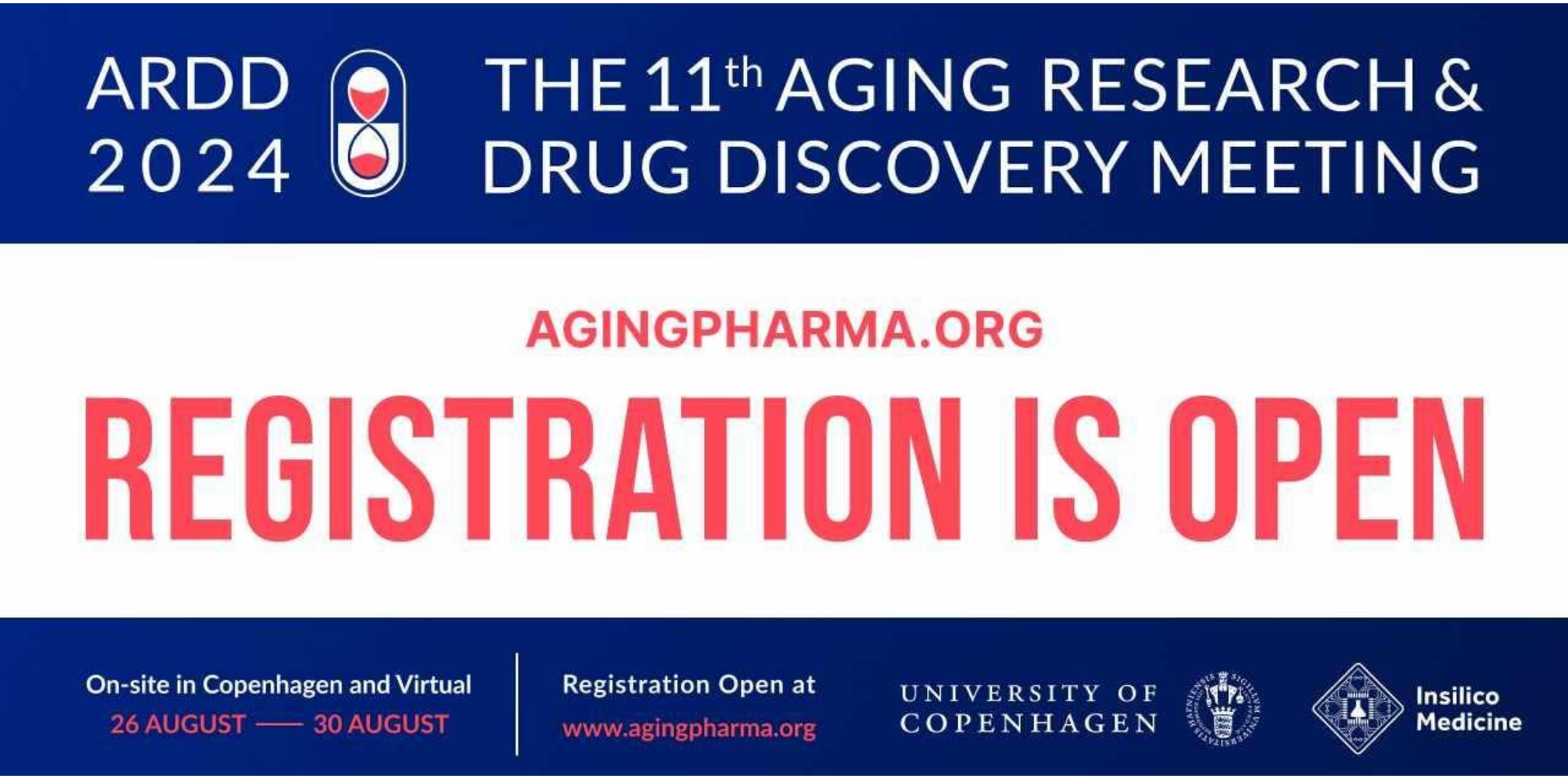

Aging research articles

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Lifespan effects in male UM-HET3 mice treated with sodium thiosulfate, 16-hydroxyestriol, and late-start canagliflozin

Genetically heterogeneous UM-HET3 mice born in 2020 were used to test possible lifespan effects of alpha-ketoglutarate (AKG), 2,4-dinitrophenol (DNP), hydralazine (HYD), nebivolol (NEBI), 16α-hydroxyestriol (OH_Est), and sodium thiosulfate (THIO), and to evaluate the effects of canagliflozin (Cana) when started at 16 months of age. OH_Est produced a 15% increase ($p = 0.0001$) in median lifespan in males but led to a significant (7%) decline in female lifespan. Cana, started at 16 months, also led to a significant increase (14%, $p = 0.004$) in males and a significant decline (6%, $p = 0.03$) in females. Cana given to mice at 6 months led, as in our previous study, to an increase in male lifespan without any change in female lifespan, suggesting that this agent may lead to female-specific late-life harm. We found that blood levels of Cana were approximately 20-fold higher in aged females than in young males, suggesting a possible mechanism for the sex-specific disparities in its effects. NEBI was also found to produce a female-specific decline (4%, $p = 0.03$) in lifespan. None of the other tested drugs provided a lifespan benefit in either sex. These data bring to 7 the list of ITP-tested drugs that induce at least a 10% lifespan increase in one or both sexes, add a fourth drug with demonstrated mid-life benefits on lifespan, and provide a testable hypothesis that might explain the sexual dimorphism in lifespan effects of the SGLT2 inhibitor Cana.

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Aging clocks based on accumulating stochastic variation

David H. Meyer & Björn Schumacher

Aging clocks have provided one of the most important recent breakthroughs in the biology of aging, and may provide indicators for the effectiveness of interventions in the aging process and preventive treatments for age-related diseases. The reproducibility of accurate aging clocks has reinvigorated the debate on whether a programmed process underlies aging. Here we show that accumulating stochastic variation in purely simulated data is sufficient to build aging clocks, and that first-generation and second-generation aging clocks are compatible with the accumulation of stochastic variation in DNA methylation or transcriptomic data. We find that accumulating stochastic variation is sufficient to predict chronological and biological age, indicated by significant prediction differences in smoking, calorie restriction, heterochronic parabiosis and partial reprogramming. Although our simulations may not explicitly rule out a programmed aging process, our results suggest that stochastically accumulating changes in any set of data that have a ground state at age zero are sufficient for generating aging clocks.

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Quantifying the stochastic component of epigenetic aging

Huige Tong, Varun B. Dwaraka, Qingwen Chen, Qi Luo, Jessica A. Lasky-Su, Ryan Smith & Andrew E. Teschendorff

DNA methylation clocks can accurately estimate chronological age and, to some extent, also biological age, yet the process by which age-associated DNA methylation (DNAm) changes are acquired appears to be quasi-stochastic, raising a fundamental question: how much of an epigenetic clock's predictive accuracy could be explained by a stochastic process of DNAm change? Here, using DNAm data from sorted immune cells, we build realistic simulation models, subsequently demonstrating in over 22,770 sorted and whole-blood samples from 25 independent cohorts that approximately 66–75% of the accuracy underpinning Horvath's clock could be driven by a stochastic process. This fraction increases to 90% for the more accurate Zhang's clock, but is lower (63%) for the PhenoAge clock, suggesting that biological aging is reflected by nonstochastic processes. Confirming this, we demonstrate that Horvath's age acceleration in males and PhenoAge's age acceleration in severe coronavirus disease 2019 cases and smokers are not driven by an increased rate of stochastic change but by nonstochastic processes. These results significantly deepen our understanding and interpretation of epigenetic clocks.

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Nature of epigenetic aging from a single-cell perspective

Andrei E. Tarkhov, Thomas Lindstrom-Vautrin, Sirui Zhang, Kejun Ying, Mahdi Moqri, Bohan Zhang, Alexander Tyshkovskiy, Orr Levy & Vadim N. Gladyshev

Age-related changes in DNA methylation (DNAm) form the basis of the most robust predictors of age—epigenetic clocks—but a clear mechanistic understanding of exactly which aspects of aging are quantified by these clocks is lacking. Here, to clarify the nature of epigenetic aging, we juxtapose the dynamics of tissue and single-cell DNAm in mice. We compare these changes during early development with those observed during adult aging in mice, and corroborate our analyses with a single-cell RNA sequencing analysis within the same multiomics dataset. We show that epigenetic aging involves co-regulated changes as well as a major stochastic component, and this is consistent with transcriptional patterns. We further support the finding of stochastic epigenetic aging by direct tissue and single-cell DNAm analyses and modeling of aging DNAm trajectories with a stochastic process akin to radiocarbon decay. Finally, we describe a single-cell algorithm for the identification of co-regulated and stochastic CpG clusters showing consistent transcriptomic coordination patterns. Together, our analyses increase our understanding of the basis of epigenetic clocks and highlight potential opportunities for targeting aging and evaluating longevity interventions.

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Using non-invasive behavioral and physiological data to measure biological age in wild baboons

Biological aging is near-ubiquitous in the animal kingdom, but its timing and pace vary between individuals and over lifespans. Prospective, individual-based studies of wild animals—especially non-human primates—help identify the social and environmental drivers of this variation by indicating the conditions and exposure windows that affect aging processes. However, measuring individual biological age in wild primates is challenging because several of the most promising methods require invasive sampling. Here, we leverage observational data on behavior and physiology, collected non-invasively from 319 wild female baboons across 2402 female-years of study, to develop a composite predictor of age: the non-invasive physiology and behavior (NPB) clock. We found that age predictions from the NPB clock explained 51% of the variation in females' known ages. Further, deviations from the clock's age predictions predicted female survival: females predicted to be older than their known ages had higher adult mortality. Finally, females who experienced harsh early-life conditions were predicted to be about 6 months older than those who grew up in more benign conditions. While the relationship between early adversity and NPB age is noisy, this estimate translates to a predicted 2–3 year reduction in mean adult lifespan in our model. A constraint of our clock is that it is tailored to data collection approaches implemented in our study population. However, many of the clock's components have analogs in other populations, suggesting that non-invasive data can provide broadly applicable insight into heterogeneity in biological age in natural populations.

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Brain-muscle communication prevents muscle aging by maintaining daily physiology

ARUN KUMAR, MIREIA VACA-DEMPERE, THOMAS MORTIMER, OLEG DERYAGIN, JACOB G. SMITH, PAUL PETRUS, KEVIN B. KORONOWSKI, CAROLINA M. GRECO, JESSICA SEGALÉS, [...], AND PURA MUÑOZ-CÁNOVES +8 authors Authors Info & Affiliations

A molecular clock network is crucial for daily physiology and maintaining organismal health. We examined the interactions and importance of intratissue clock networks in muscle tissue maintenance. In arrhythmic mice showing premature aging, we created a basic clock module involving a central and a peripheral (muscle) clock. Reconstituting the brain-muscle clock network is sufficient to preserve fundamental daily homeostatic functions and prevent premature muscle aging. However, achieving whole muscle physiology requires contributions from other peripheral clocks. Mechanistically, the muscle peripheral clock acts as a gatekeeper, selectively suppressing detrimental signals from the central clock while integrating important muscle homeostatic functions. Our research reveals the interplay between the central and peripheral clocks in daily muscle function and underscores the impact of eating patterns on these interactions.

Outrunning the grim reaper: longevity of the first 200 sub-4 min mile male runners

Stephen Foulkes [1, 2], Dean Hewitt [1], Rachel Skow [1], Douglas Dover [3], Padma Kaul [3], André La Gerche [2, 4], Mark Haykowsky [1]

Objectives To determine the impact of running a sub-4 min mile on longevity. It was hypothesised that there would be an increase in longevity for runners who successfully completed a sub-4 min mile compared with the general population.

Methods As part of this retrospective cohort study, the Sub-4 Alphabetic Register was used to extract the first 200 athletes to run a sub-4 min mile. Each runner's date of birth, date of their first successful mile attempt, current age (if alive) or age at death was compared with the United Nations Life Tables to determine the difference in each runner's current age or age at death with their country of origin-specific life expectancy.

Results Of the first 200 sub-4 min mile runners (100% male), 60 were dead (30%) and 140 were still alive. Sub-4 min mile runners lived an average of 4.7 years beyond their predicted life expectancy (95% CI 4.7 to 4.8). When accounting for the decade of completion (1950s, 1960s or 1970s), the longevity benefits were 9.2 years (n=22; 95% CI 8.3 to 10.1), 5.5 years (n=88; 95% CI 5.3 to 5.7) and 2.9 years (n=90; 95% CI 2.7 to 3.1), respectively.

Conclusion Sub-4 min mile runners have increased longevity compared with the general population, thereby challenging the notion that extreme endurance exercise may be detrimental to longevity.

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Genetically determined blood pressure, antihypertensive drug classes, and frailty: A Mendelian randomization study

Zhenhuang Zhuang, Yueying Li, Yimin Zhao, Ninghao Huang, Wenxiu Wang, Wendi Xiao, Jie Du, Xue Dong, Zimin Song, Jinzhu Jia, Zhonghua Liu, Robert Clarke, Lu Qi, Tao Huang

Observational studies have suggested that the use of antihypertensive drugs was associated with the risk of frailty; however, these findings may be biased by confounding and reverse causality. This study aimed to explore the effect of genetically predicted lifelong lowering blood pressure (BP) through different antihypertensive medications on frailty. One-sample Mendelian randomization (MR) and summary data-based MR (SMR) were applied. We utilized two kinds of genetic instruments to proxy the antihypertensive medications, including genetic variants within or nearby drugs target genes associated with systolic/diastolic BP, and expression level of the corresponding gene. Among 298,618 UK Biobank participants, one-sample MR analysis observed that genetically proxied BB use (relative risk ratios, 0.76; 95% CI, 0.65–0.90; $p = 0.001$) and CCB use (0.83; 0.72–0.95; $p = 0.007$), equivalent to a 10-mm Hg reduction in systolic BP, was significantly associated with lower risk of pre-frailty. In addition, although not statistically significant, the effect directions of systolic BP through ACEi variants (0.72; 0.39–1.33; $p = 0.296$) or thiazides variants (0.74; 0.53–1.03; $p = 0.072$) on pre-frailty were also protective. Similar results were obtained in analyses for diastolic BP. SMR of expression in artery showed that decreased expression level of KCNH2, a target gene of BBs, was associated with lower frailty index (beta −0.02, $p = 2.87 \times 10^{-4}$). This MR analysis found evidence that the use of BBs and CCBs was potentially associated with reduced frailty risk in the general population, and identified KCNH2 as a promising target for further clinical trials to prevent manifestations of frailty.

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PREPRINT

In vivo reprogramming of *Caenorhabditis elegans* leads to heterogeneous effects on lifespan

Nibrasul Kamaludeen, Yann Mauge, Sonia El Mouridi, Sara Picó, Alba Vílchez-Acosta, João Agostinho de Sousa, Marie Pierron, Viviane Praz, Ferdinand von Meyenn, Christian Frøkjær-Jensen, Alejandro Ocampo

In the last decade, cellular reprogramming of fully differentiated cells to pluripotent stem cells has become of great interest. Importantly, cellular reprogramming by expression of Oct4, Sox2, Klf4, and cMyc (OSKM) can ameliorate age-associated phenotypes in multiple tissues and extend lifespan in progeroid and aged wild-type mice. Surprisingly, the effects of in vivo reprogramming have not been deeply investigated in any other model organisms. Here, for the first time, we induce in vivo reprogramming in *C. elegans* using a heat-inducible system at multiple developmental and adult stages. Similar to mice, expression of the reprogramming factors leads to premature death with different levels of toxicity at distinct developmental stages and aging. In vivo reprogramming in *C. elegans* might represent a valuable tool to improve our understanding of development and in vivo reprogramming.

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PREPRINT

Age-Invariant Genes: Multi-Tissue Identification and Characterization of Murine Reference Genes

John T. González, Kyra Thrush, Margarita Meer, Morgan E. Levine, Albert T. Higgins-Chen

Studies of the aging transcriptome focus on genes that change with age. But what can we learn from age-invariant genes—those that remain unchanged throughout the aging process? These genes also have a practical application: they serve as reference genes (often called housekeeping genes) in expression studies. Reference genes have mostly been identified and validated in young organisms, and no systematic investigation has been done across the lifespan. Here, we build upon a common pipeline for identifying reference genes in RNA-seq datasets to identify age-invariant genes across seventeen C57BL/6 mouse tissues (brain, lung, bone marrow, muscle, white blood cells, heart, small intestine, kidney, liver, pancreas, skin, brown, gonadal, marrow, and subcutaneous adipose tissue) spanning 1 to 21+ months of age. We identify 9 pan-tissue age-invariant genes and many tissue-specific age-invariant genes. These genes are stable across the lifespan and are validated in independent bulk RNA-seq datasets and RT-qPCR. We find age-invariant genes have shorter transcripts on average and are enriched for CpG islands. Interestingly, pathway enrichment analysis for age-invariant genes identifies an overrepresentation of molecular functions associated with some, but not all, hallmarks of aging. Thus, though hallmarks of aging typically involve changes in cell maintenance mechanisms, select genes associated with these hallmarks resist fluctuations in expression with age. Finally, our analysis concludes no classical reference gene is appropriate for aging studies in all tissues. Instead, we provide tissue-specific and pan-tissue genes for assays utilizing reference gene normalization (i.e., RT-qPCR) that can be applied to animals across the lifespan.

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PREPRINT

Pleiotropy and Disease Interactors: The Dual Nature of Genes Linking Ageing and Ageing-related Diseases

Gustavo Daniel Vega Magdaleno, Joao Pedro de Magalhaes

Ageing-related diseases (ARDs) exhibit a broad spectrum of phenotypes yet consistently increase in incidence with advancing age. This suggests that, despite their diversity, ARDs could potentially share common biological processes deeply rooted in the mechanisms of ageing, presenting opportunities for unified therapeutic strategies. Using a network approach, we analysed gene proximity to 52 ARDs from the UK Biobank, integrating with protein-protein interaction (PPI), gene coexpression, KEGG pathways, and ageing-related genes. Interestingly, while most ageing-related genes did not associate with ARDs, they were closer to multiple ARDs than random genes. This was mainly due to indirect connections to diverse Communities of ARDs (ARCs), what we call *iARC-Interactors*, implying indirect association to multiple ARDs through interaction with ARD-related genes, primarily via PPI and KEGG. Genes that are associated with multiple ARCs, *i.e.*, *Pleiotropic* genes, were predominantly related to immunological disorders. We found a polarizing effect. When compared to multiple ageing- and disease-related genes, high *Pleiotropic* genes showed the highest tissue specificity and lowest coexpression with themselves and other diseases. In contrast, high i*ARC-interactive* genes (as those of ageing) significantly displayed the exact opposite effects, suggesting two mechanisms for genes to affect multiple ARDs, one operating through modulatory genes that simultaneously affect numerous tissues and processes; and another rather specialised, affecting single tissues that are widespread across the body, as potentially occurring in autoimmune diseases. Lastly, we used Machine Learning (ML) to predict potentially novel ageing-related genes based on each network's *iARC-Interactions* and genes' proximity to ARDs. PPI and KEGG showed the best performance with their top candidate genes enriched for regulation of protein metabolic process, protein stabilization, positive regulation of developmental process, and cellular response to chemical stimulus. This work paints a deeper picture of the multiple types of interactions between ageing-related processes and ARDs.

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Senolytic Therapy Enabled by Senescent Cell-Sensitive Biomimetic Melanin Nano-senolytics

Hairui Zhang, Xiaoling Xu, Xin Shou, Wucan Liao, Chengkang Jin, Changjiang Chen, Chen Zhang, Wenhua Gao, Junfeng Zhang, Weihong Ge, Liyun Shi

Cellular senescence is a significant risk factor for aging and age-related diseases (ARD). The canonical senolytics Dasatinib and Quercetin (DQ) have shown promise in clearing senescent cells (SnCs); however, the lack of selectivity poses a challenge in achieving optimal outcomes. Despite the recent occurrence of the nanomaterial-based approaches targeting SnCs, limited therapeutic effects and potential toxicity still remain a major concern. Herein, we developed a "double locks-like" nanoplatform that integrated Galactan coating and mesoporous polydopamine to encase the senolytic drug DQ. By this way, DQ was only released in SnCs that were featured with higher levels of β-galactosidase (β-gal) and low PH. Additionally, the nanoparticles were equipped with 2,2,6,6-Tetramethylpiperidine-1-oxyl (Tempo) to gain enhanced photothermal converting potential. Consequently, the synthesized nanosenolytics demonstrated remarkable specificity and efficacy in eradicating SnCs, and accordingly reversed pulmonary fibrosis in mice without affecting normal tissues. Upon exposure of near-infrared (NIR) light, the nanoparticles demonstrated to efficiently remove senescent tumor cells inducted by chemotherapy, thereby hindering the outgrowth and metastasis or breast cancer. Collectively, the present study develops an "On/Off" switchable nanoplatform in response to SnCs, and produces a more safe, efficient and feasible way to delay aging or alleviate age-associated diseases.

Failure of senolytic treatment to prevent cognitive decline in a female rodent model of aging

Asha Rani [1], Linda Bean [1], Vivekananda Budamagunta [1 2 3], Ashok Kumar [1], Thomas C Foster [1 2]

There are sex differences in vulnerability and resilience to the stressors of aging and subsequent age-related cognitive decline. Cellular senescence occurs as a response to damaging or stress-inducing stimuli. The response includes a state of irreversible growth arrest, the development of a senescence-associated secretory phenotype, and the release of pro-inflammatory cytokines associated with aging and age-related diseases. Senolytics are compounds designed to eliminate senescent cells. Our recent work indicates that senolytic treatment preserves cognitive function in aging male F344 rats. The current study examined the effect of senolytic treatment on cognitive function in aging female rats. Female F344 rats (12 months) were treated with dasatinib (1.2 mg/kg) + quercetin (12 mg/kg) or ABT-263 (12 mg/kg) or vehicle for 7 months. Examination of the estrus cycle indicated that females had undergone estropause during treatment. Senolytic treatment may have increased sex differences in behavioral stress responsivity, particularly for the initial training on the cued version of the watermaze. However, pre-training on the cue task reduced stress responsivity for subsequent spatial training and all groups learned the spatial discrimination. In contrast to preserved memory observed in senolytic-treated males, all older females exhibited impaired episodic memory relative to young (6-month) females. We suggest that the senolytic treatment may not have been able to compensate for the loss of estradiol, which can act on aging mechanisms for anxiety and memory independent of cellular senescence.

The molecular evolution of cancer associated genes in mammals

Nick MacDonald, Nynke Raven, Wendy Diep, Samantha Evans, Senuri Pannipitiya, Georgina Bramwell, Caitlin Vanbeek, Frédéric Thomas, Tracey Russell, Antoine M. Dujon, Marina Telonis-Scott & Beata Ujvari

Cancer is a disease that many multicellular organisms have faced for millions of years, and species have evolved various tumour suppression mechanisms to control oncogenesis. Although cancer occurs across the tree of life, cancer related mortality risks vary across mammalian orders, with Carnivorans particularly affected. Evolutionary theory predicts different selection pressures on genes associated with cancer progression and suppression, including oncogenes, tumour suppressor genes and immune genes. Therefore, we investigated the evolutionary history of cancer associated gene sequences across 384 mammalian taxa, to detect signatures of selection across categories of oncogenes (GRB2, FGL2 and CDC42), tumour suppressors (LITAF, Casp8 and BRCA2) and immune genes (IL2, CD274 and B2M). This approach allowed us to conduct a fine scale analysis of gene wide and site-specific signatures of selection across mammalian lineages under the lens of cancer susceptibility. Phylogenetic analyses revealed that for most species the evolution of cancer associated genes follows the species' evolution. The gene wide selection analyses revealed oncogenes being the most conserved, tumour suppressor and immune genes having similar amounts of episodic diversifying selection. Despite BRCA2's status as a key caretaker gene, episodic diversifying selection was detected across mammals. The site-specific selection analyses revealed that the two apoptosis associated domains of the Casp8 gene of bats (Chiroptera) are under opposing forces of selection (positive and negative respectively), highlighting the importance of site-specific selection analyses to understand the evolution of highly complex gene families. Our results highlighted the need to critically assess different types of selection pressure on cancer associated genes when investigating evolutionary adaptations to cancer across the tree of life. This study provides an extensive assessment of cancer associated genes in mammals with highly representative, and substantially large sample size for a comparative genomic analysis in the field and identifies various avenues for future research into the mechanisms of cancer resistance and susceptibility in mammals.

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PREPRINT

A metabolic atlas of mouse aging

Steven E Pilley, Dominik Awad, Djakim Latumalea, Edgar Esparza, Li Zhang, Xuanyi Shi, Maximilian Unfried, Shuo Wang, Racheal Mulondo, Sriraksha Bharadwaj Kashyap, Darius Moaddeli, Peter Sajjakulnukit, Damien Sutton, Harrison Wong, Aeowynn J. Coakley, Gilberto Garcia, Ryo Higuchi-Sanabria, Sophia Liu, Bingfei Yu, William B Tu, Brian K. Kennedy, Costas A Lyssiotis, Peter J Mullen

Humans are living longer, but this is accompanied by an increased incidence of age-related chronic diseases. Many of these diseases are influenced by age-associated metabolic dysregulation, but how metabolism changes in multiple organs during aging in males and females is not known. Answering this could reveal new mechanisms of aging and age-targeted therapeutics. In this study, we describe how metabolism changes in 12 organs in male and female mice at 5 different ages. Organs show distinct patterns of metabolic aging that are affected by sex differently. Hydroxyproline shows the most consistent change across the dataset, decreasing with age in 11 out of 12 organs investigated. We also developed a metabolic aging clock that predicts biological age and identified alpha-ketoglutarate, previously shown to extend lifespan in mice, as a key predictor of age. Our results reveal fundamental insights into the aging process and identify new therapeutic targets to maintain organ health.

C. elegans aging research

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Fmo induction as a tool to screen for pro-longevity drugs

Dietary restriction (DR) and hypoxia (low oxygen) extend lifespan in *Caenorhabditis elegans* through the induction of a convergent downstream longevity gene, *fmo-2*. Flavin-containing monooxygenases (FMOs) are highly conserved xenobiotic-metabolizing enzymes with a clear role in promoting longevity in nematodes and a plausible similar role in mammals. This makes them an attractive potential target of small molecule drugs to stimulate the health-promoting effects of longevity pathways. Here, we utilize an *fmo-2* fluorescent transcriptional reporter in *C. elegans* to screen a set of 80 compounds previously shown to improve stress resistance in mouse fibroblasts. Our data show that 19 compounds significantly induce *fmo-2*, and 10 of the compounds induce *fmo-2* more than twofold. Interestingly, 9 of the 10 high *fmo-2* inducers also extend lifespan in *C. elegans*. Two of these drugs, mitochondrial respiration chain complex inhibitors, interact with the hypoxia pathway to induce *fmo-2*, whereas two dopamine receptor type 2 (DRD2) antagonists interact with the DR pathway to induce *fmo-2*, indicating that dopamine signaling is involved in DR-mediated *fmo-2* induction. Together, our data identify nine drugs that each (1) increase stress resistance in mouse fibroblasts, (2) induce *fmo-2* in *C. elegans*, and (3) extend nematode lifespan, some through known longevity pathways. These results define *fmo-2* induction as a viable approach to identifying and understanding mechanisms of putative longevity compounds.

REVIEWS/COMMENTS/ METHODS/EDITORIALS

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Editorial | Published: 27 May 2024

Gerogenes and gerosuppression: the pillars of precision geromedicine

Carlos López-Otín, Andrea B. Maier & Guido Kroemer

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213 Accesses | Metrics

Tumorigenesis is driven by the gain-of-function mutation or overexpression of oncogenes, as well as by the inactivation of oncosuppresssive (tumor suppressor) genes due to their loss-of-function mutation, genomic loss, or epigenetic silencing. This combination of factors increases the cell-intrinsic fitness of malignant cells, enhances their capacity to obtain trophic support by the tumor microenvironment, and simultaneously subverts cancer immunosurveillance.[1] Since the realization that neoplasia is driven by molecularly defined genetic alterations, cancer is not more conceived as a fatality but as a disease that — at least theoretically — can be targeted by inhibiting oncogenes or reestablishing oncosuppression within the realm of 'precision oncology'. Indeed, at the oncological ward, deep sequencing of tumor DNA and RNA has become part of the clinical routine to retrieve information on genomic, epigenomic, and transcriptomic alterations and hence to identify patients who may benefit from specific drugs targeting relevant pathways.[2]

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Translatability of life-extending pharmacological treatments between different species

Daiana Burdusel [1 2], Cristin Coman [3], Diana-Larisa Ancuta [3], Dirk Hermann [2], Thorsten Doeppner [4 5], Andrei Gresita [6], Aurel Popa-Wagner [1 2]

Affiliations + expand

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Abstract

Anti-aging research has made significant strides in identifying treatments capable of extending lifespan across a range of organisms, from simple invertebrates to mammals. This review showcases the current state of anti-aging interventions, highlighting the lifespan extensions observed in animal models through various treatments and the challenges encountered in translating these findings to humans. Despite promising results in lower organisms, the translation of anti-aging treatments to human applications presents a considerable challenge. This discrepancy can be attributed to the increasing complexity of biological systems, species-specific metabolic and genetic differences, and the redundancy of metabolic pathways linked to longevity. Our review focuses on analyzing these challenges, offering insights into the efficacy of anti-aging mechanisms across species and identifying key barriers to their translation into human treatments. By synthesizing current knowledge and identifying gaps in translatability, this review aims to underscore the importance of advancing these therapies for human benefit. Bridging this gap is essential to assess the potential of such treatments in extending the human healthspan.

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How does a fly die? Insights into ageing from the pathophysiology of *Drosophila* mortality

The fruit fly *Drosophila melanogaster* is a common animal model in ageing research. Large populations of flies are used to study the impact of genetic, nutritional and pharmacological interventions on survival. However, the processes through which flies die and their relative prevalence in *Drosophila* populations are still comparatively unknown. Understanding the causes of death in an animal model is essential to dissect the lifespan-extending interventions that are organism- or disease-specific from those broadly applicable to ageing. Here, we review the pathophysiological processes that can lead to fly death and discuss their relation to ageing.

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Autophagy and machine learning: Unanswered questions

Ying Yang [a b c d 1], Zhaoying Pan [c 1], Jianhui Sun [e], Joshua Welch [c d], Daniel J. Klionsky [a b]

Autophagy is a critical conserved cellular process in maintaining cellular homeostasis by clearing and recycling damaged organelles and intracellular components in lysosomes and vacuoles. Autophagy plays a vital role in cell survival, bioenergetic homeostasis, organism development, and cell death regulation. Malfunctions in autophagy are associated with various human diseases and health disorders, such as cancers and neurodegenerative diseases. Significant effort has been devoted to autophagy-related research in the context of genes, proteins, diagnosis, etc. In recent years, there has been a surge of studies utilizing state of the art machine learning (ML) tools to analyze and understand the roles of autophagy in various biological processes. We taxonomize ML techniques that are applicable in an autophagy context, comprehensively review existing efforts being taken in this direction, and outline principles to consider in a biomedical context. In recognition of recent groundbreaking advances in the deep-learning community, we discuss new opportunities in interdisciplinary collaborations and seek to engage autophagy and computer science researchers to promote autophagy research with joint efforts.

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Amino acid restriction, aging, and longevity: an update

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Affiliations + expand

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Abstract

Various so-called dietary restriction paradigms have shown promise for extending health and life. All such paradigms rely on *ad libitum* (hereafter *ad lib*) feeding, something virtually never employed in animals whose long-term health we value, either as a control or, except for food restriction itself, for both control and treatment arms of the experiment. Even though the mechanism(s) remain only vaguely understood, compared to *ad lib*-fed animals a host of dietary manipulations, including calorie restriction, low protein, methionine, branched-chain amino acids, and even low isoleucine have demonstrable health benefits in laboratory species in a standard laboratory environment. The remaining challenge is to determine whether these health benefits remain in more realistic environments and how they interact with other health enhancing treatments such as exercise or emerging geroprotective drugs. Here we review the current state of the field of amino acid restriction on longevity of animal models and evaluate its translational potential.

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Aging and cancer

Léa Montégut [1 2], Carlos López-Otín [1 3], Guido Kroemer [4 5 6]

Affiliations + expand

PMID: 38760832 PMCID: PMC11102267 DOI: 10.1186/s12943-024-02020-z

Abstract

Aging and cancer exhibit apparent links that we will examine in this review. The null hypothesis that aging and cancer coincide because both are driven by time, irrespective of the precise causes, can be confronted with the idea that aging and cancer share common mechanistic grounds that are referred to as 'hallmarks'. Indeed, several hallmarks of aging also contribute to carcinogenesis and tumor progression, but some of the molecular and cellular characteristics of aging may also reduce the probability of developing lethal cancer, perhaps explaining why very old age (> 90 years) is accompanied by a reduced incidence of neoplastic diseases. We will also discuss the possibility that the aging process itself causes cancer, meaning that the time-dependent degradation of cellular and supracellular functions that accompanies aging produces cancer as a byproduct or 'age-associated disease'. Conversely, cancer and its treatment may erode health and drive the aging process, as this has dramatically been documented for cancer survivors diagnosed during childhood, adolescence, and young adulthood. We conclude that aging and cancer are connected by common superior causes including endogenous and lifestyle factors, as well as by a bidirectional crosstalk, that together render old age not only a risk factor of cancer but also an important parameter that must be considered for therapeutic decisions.

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CD4+ T-Cell Senescence in Neurodegenerative Disease: Pathogenesis and Potential Therapeutic Targets

by Yan Gao †, Yaoping Lu †, Xiaojing Liang, Mengwei Zhao, Xinyue Yu, Haiying Fu and Wei Yang *

With the increasing proportion of the aging population, neurodegenerative diseases have become one of the major health issues in society. Neurodegenerative diseases (NDs), including multiple sclerosis (MS), Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS), are characterized by progressive neurodegeneration associated with aging, leading to a gradual decline in cognitive, emotional, and motor functions in patients. The process of aging is a normal physiological process in human life and is accompanied by the aging of the immune system, which is known as immunosenescence. T-cells are an important part of the immune system, and their senescence is the main feature of immunosenescence. The appearance of senescent T-cells has been shown to potentially lead to chronic inflammation and tissue damage, with some studies indicating a direct link between T-cell senescence, inflammation, and neuronal damage. The role of these subsets with different functions in NDs is still under debate. A growing body of evidence suggests that in people with a ND, there is a prevalence of CD4+ T-cell subsets exhibiting characteristics that are linked to senescence. This underscores the significance of CD4+ T-cells in NDs. In this review, we summarize the classification and function of CD4+ T-cell subpopulations, the characteristics of CD4+ T-cell senescence, the potential roles of these cells in animal models and human studies of NDs, and therapeutic strategies targeting CD4+ T-cell senescence.

OTHER RESEARCH & REVIEWS

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Topic of this month's journal club!

Ketogenic diet induces p53-dependent cellular senescence in multiple organs

A ketogenic diet (KD) is a high-fat, low-carbohydrate diet that leads to the generation of ketones. While KDs improve certain health conditions and are popular for weight loss, detrimental effects have also been reported. Here, we show mice on two different KDs and, at different ages, induce cellular senescence in multiple organs, including the heart and kidney. This effect is mediated through adenosine monophosphate–activated protein kinase (AMPK) and inactivation of mouse double minute 2 (MDM2) by caspase-2, leading to p53 accumulation and p21 induction. This was established using p53 and caspase-2 knockout mice and inhibitors to AMPK, p21, and caspase-2. In addition, senescence-associated secretory phenotype biomarkers were elevated in serum from mice on a KD and in plasma samples from patients on a KD clinical trial. Cellular senescence was eliminated by a senolytic and prevented by an intermittent KD. These results have important clinical implications, suggesting that the effects of a KD are contextual and likely require individual optimization.

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The complete sequence and comparative analysis of ape sex chromosomes

Apes possess two sex chromosomes—the male-specific Y chromosome and the X chromosome, which is present in both males and females. The Y chromosome is crucial for male reproduction, with deletions being linked to infertility[1]. The X chromosome is vital for reproduction and cognition[2]. Variation in mating patterns and brain function among apes suggests corresponding differences in their sex chromosomes. However, owing to their repetitive nature and incomplete reference assemblies, ape sex chromosomes have been challenging to study. Here, using the methodology developed for the telomere-to-telomere (T2T) human genome, we produced gapless assemblies of the X and Y chromosomes for five great apes (bonobo (*Pan paniscus*), chimpanzee (*Pan troglodytes*), western lowland gorilla (*Gorilla gorilla gorilla*), Bornean orangutan (*Pongo pygmaeus*) and Sumatran orangutan (*Pongo abelii*)) and a lesser ape (the siamang gibbon (*Symphalangus syndactylus*)), and untangled the intricacies of their evolution. Compared with the X chromosomes, the ape Y chromosomes vary greatly in size and have low alignability and high levels of structural rearrangements—owing to the accumulation of lineage-specific ampliconic regions, palindromes, transposable elements and satellites. Many Y chromosome genes expand in multi-copy families and some evolve under purifying selection. Thus, the Y chromosome exhibits dynamic evolution, whereas the X chromosome is more stable. Mapping short-read sequencing data to these assemblies revealed diversity and selection patterns on sex chromosomes of more than 100 individual great apes. These reference assemblies are expected to inform human evolution and conservation genetics of non-human apes, all of which are endangered species.

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PREPRINT

The role of Mediterranean diet in cancer incidence and mortality in the older adults: a systematic review and meta-analysis.

Giulia Giordano, Luca Mastrantoni, Roberta Terranova, Giuseppe Colloca, and 2 more

The magnitude of benefit of Mediterranean diet in cancer prevention and mortality in older adults is still unclear, therefore we conducted a systematic review and meta-analysis. Outcomes considered were cancer incidence and cancer mortality.

In studies evaluating cancer incidence as a time-to-event endpoint and adherence as quantiles, HR was 0.885 (95% CI 0.773–1.013, $I^2 = 44\%$). Including ORs, exploratory pooled effect size was 0.876 (0.794–0.966, $I^2 = 34\%$), consistently with results of studies evaluating ORs for adherence as one-point increase (OR 0.744, 0.570–0.972, $I^2 = 90\%$). No clear benefit was observed on cancer mortality, with pooled HR of 0.935 (0.800-1.093, $I^2 = 0\%$). Significant interaction was observed for ORs according to cancer type but not between medium and high adherence for both outcomes.

Our findings suggest that MD plays a protective role in cancer incidence in advanced age, but no clear effect on cancer mortality was observed.

Food additive emulsifiers and cancer risk: Results from the French prospective NutriNet-Santé cohort

Methods and findings

This study included 92,000 adults of the French NutriNet-Santé cohort without prevalent cancer at enrolment (44.5 y [SD: 14.5], 78.8% female, 2009 to 2021). They were followed for an average of 6.7 years [SD: 2.2]. Food additive emulsifier intakes were estimated for participants who provided at least 3 repeated 24-h dietary records linked to comprehensive, brand-specific food composition databases on food additives. Multivariable Cox regressions were conducted to estimate associations between emulsifiers and cancer incidence. Overall, 2,604 incident cancer cases were diagnosed during follow-up (including 750 breast, 322 prostate, and 207 colorectal cancers). Higher intakes of mono- and diglycerides of fatty acids (FAs) (E471) were associated with higher risks of overall cancer ($HR_{\text{high vs. low category}}$ = 1.15; 95% CI [1.04, 1.27], p-trend = 0.01), breast cancer (HR = 1.24; 95% CI [1.03, 1.51], p-trend = 0.04), and prostate cancer (HR = 1.46; 95% CI [1.09, 1.97], p-trend = 0.02). In addition, associations with breast cancer risk were observed for higher intakes of total carrageenans (E407 and E407a) (HR = 1.32; 95% CI [1.09, 1.60], p-trend = 0.009) and carrageenan (E407) (HR = 1.28; 95% CI [1.06, 1.56], p-trend = 0.01). No association was detected between any of the emulsifiers and colorectal cancer risk. Several associations with other emulsifiers were observed but were not robust throughout sensitivity analyses. Main limitations include possible exposure measurement errors in emulsifiers intake and potential residual confounding linked to the observational design.