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Scientific News
3rd of February 2024
Sven Bulterijs

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Business/Conferences/ General news

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Global cancer burden growing, amidst mounting need for services

1 February 2024 | News release | Lyon, France; Geneva, Switzerland |Reading time: 4 min (1192 words)

Ahead of World Cancer Day, the World Health Organization (WHO)'s cancer agency, the International Agency for Research on Cancer (IARC), released the latest estimates of the global burden of cancer. WHO also published survey results from 115 countries, showing a majority of countries do not adequately finance priority cancer and palliative care services, as part of universal health coverage (UHC).

Over 35 million new cancer cases are predicted in 2050, a 77% increase from the estimated 20 million cases in 2022. The rapidly growing global cancer burden reflects both population ageing and growth, as well as changes to people's exposure to risk factors, several of which are associated with socioeconomic development. Tobacco, alcohol and obesity are key factors behind the increasing incidence of cancer, with air pollution still a key driver of environmental risk factors.

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Biogen abandons Aduhelm efforts, focuses on Eisai-partnered Leqembi and pipeline drugs

By **Eric Sagonowsky** · Jan 31, 2024 8:35am

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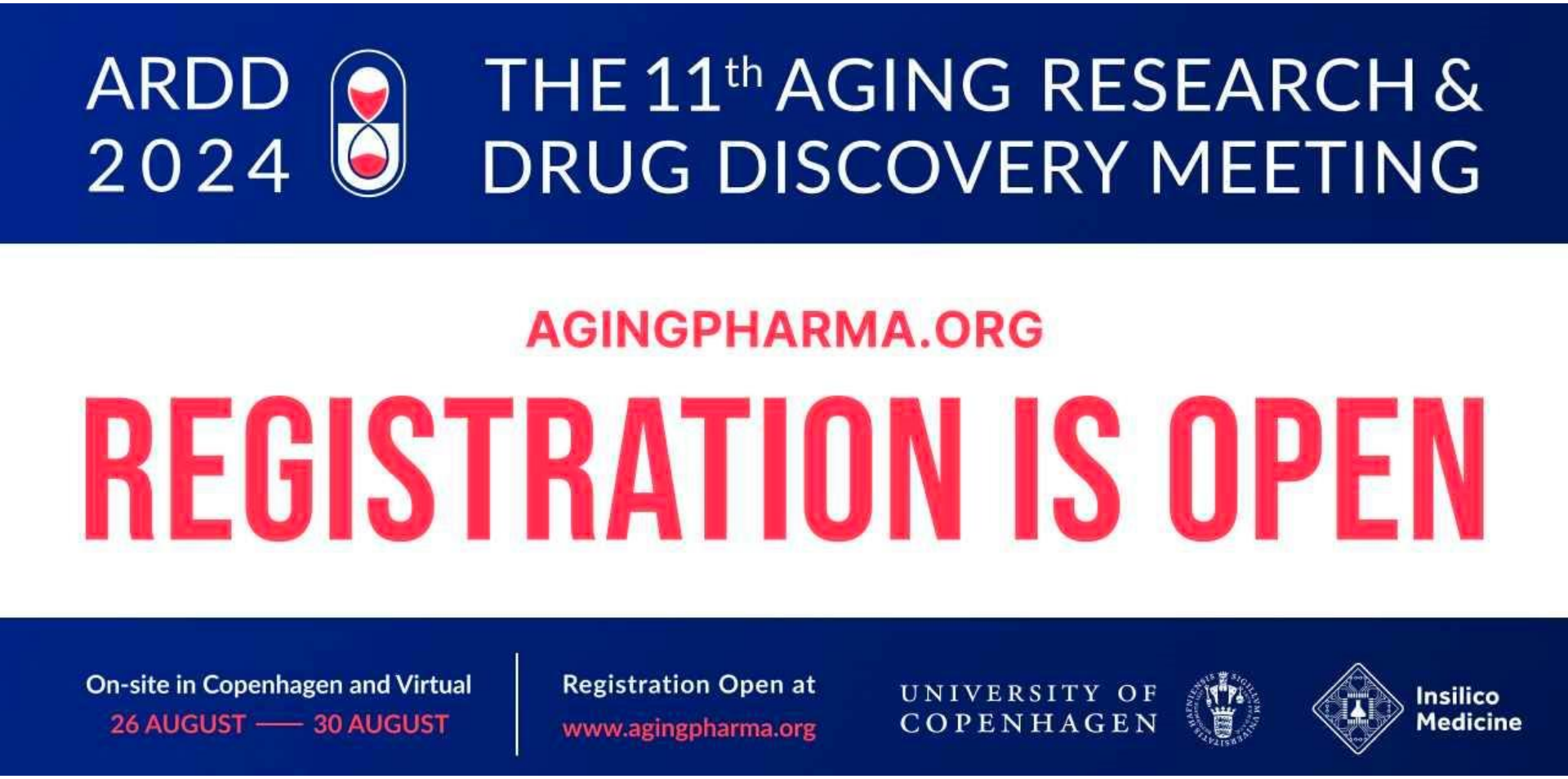

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Aging research articles

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Causality-enriched epigenetic age uncouples damage and adaptation

Kejun Ying, Hanna Liu, Andrei E. Tarkhov, Marie C. Sadler, Ake T. Lu, Mahdi Moqri, Steve Horvath, Zoltán Kutalik, Xia Shen & Vadim N. Gladyshev

Machine learning models based on DNA methylation data can predict biological age but often lack causal insights. By harnessing large-scale genetic data through epigenome-wide Mendelian randomization, we identified CpG sites potentially causal for aging-related traits. Neither the existing epigenetic clocks nor age-related differential DNA methylation are enriched in these sites. These CpGs include sites that contribute to aging and protect against it, yet their combined contribution negatively affects age-related traits. We established a new framework to introduce causal information into epigenetic clocks, resulting in DamAge and AdaptAge—clocks that track detrimental and adaptive methylation changes, respectively. DamAge correlates with adverse outcomes, including mortality, while AdaptAge is associated with beneficial adaptations. These causality-enriched clocks exhibit sensitivity to short-term interventions. Our findings provide a detailed landscape of CpG sites with putative causal links to lifespan and healthspan, facilitating the development of aging biomarkers, assessing interventions, and studying reversibility of age-associated changes.

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Prophylactic and long-lasting efficacy of senolytic CAR T cells against age-related metabolic dysfunction

Senescent cells, which accumulate in organisms over time, contribute to age-related tissue decline. Genetic ablation of senescent cells can ameliorate various age-related pathologies, including metabolic dysfunction and decreased physical fitness. While small-molecule drugs that eliminate senescent cells ('senolytics') partially replicate these phenotypes, they require continuous administration. We have developed a senolytic therapy based on chimeric antigen receptor (CAR) T cells targeting the senescence-associated protein urokinase plasminogen activator receptor (uPAR), and we previously showed these can safely eliminate senescent cells in young animals. We now show that uPAR-positive senescent cells accumulate during aging and that they can be safely targeted with senolytic CAR T cells. Treatment with anti-uPAR CAR T cells improves exercise capacity in physiological aging, and it ameliorates metabolic dysfunction (for example, improving glucose tolerance) in aged mice and in mice on a high-fat diet. Importantly, a single administration of these senolytic CAR T cells is sufficient to achieve long-term therapeutic and preventive effects.

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A drug cocktail of rapamycin, acarbose, and phenylbutyrate enhances resilience to features of early-stage Alzheimer's disease in aging mice

The process of aging is defined by the breakdown of critical maintenance pathways leading to an accumulation of damage and its associated phenotypes. Aging affects many systems and is considered the greatest risk factor for a number of diseases. Therefore, interventions aimed at establishing resilience to aging should delay or prevent the onset of age-related diseases. Recent studies have shown a three-drug cocktail consisting of rapamycin, acarbose, and phenylbutyrate delayed the onset of physical, cognitive, and biological aging phenotypes in old mice. To test the ability of this drug cocktail to impact Alzheimer's disease (AD), an adeno-associated-viral vector model of AD was created. Mice were fed the drug cocktail 2 months prior to injection and allowed 3 months for phenotypic development. Cognitive phenotypes were evaluated through a spatial navigation learning task. To quantify neuropathology, immunohistochemistry was performed for AD proteins and pathways of aging. Results suggested the drug cocktail was able to increase resilience to cognitive impairment, inflammation, and AD protein aggregation while enhancing autophagy and synaptic integrity, preferentially in female cohorts. In conclusion, female mice were more susceptible to the development of early stage AD neuropathology and learning impairment, and more responsive to treatment with the drug cocktail in comparison to male mice. Translationally, a model of AD where females are more susceptible would have greater value as women have a greater burden and incidence of disease compared to men. These findings validate past results and provide the rationale for further investigations into enhancing resilience to early-stage AD by enhancing resilience to aging.

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Depletion of SAM leading to loss of heterochromatin drives muscle stem cell ageing

Jengmin Kang, Daniel I. Benjamin, Soochi Kim, Jayesh S. Salvi, Gurkamal Dhaliwal, Richard Lam, Armon Goshayeshi, Jamie O. Brett, Ling Liu & Thomas A. Rando

The global loss of heterochromatin during ageing has been observed in eukaryotes from yeast to humans, and this has been proposed as one of the causes of ageing. However, the cause of this age-associated loss of heterochromatin has remained enigmatic. Here we show that heterochromatin markers, including histone H3K9 di/tri-methylation and HP1, decrease with age in muscle stem cells (MuSCs) as a consequence of the depletion of the methyl donor S-adenosylmethionine (SAM). We find that restoration of intracellular SAM in aged MuSCs restores heterochromatin content to youthful levels and rejuvenates age-associated features, including DNA damage accumulation, increased cell death, and defective muscle regeneration. SAM is not only a methyl group donor for transmethylation, but it is also an aminopropyl donor for polyamine synthesis. Excessive consumption of SAM in polyamine synthesis may reduce its availability for transmethylation. Consistent with this premise, we observe that perturbation of increased polyamine synthesis by inhibiting spermidine synthase restores intracellular SAM content and heterochromatin formation, leading to improvements in aged MuSC function and regenerative capacity in male and female mice. Together, our studies demonstrate a direct causal link between polyamine metabolism and epigenetic dysregulation during murine MuSC ageing.

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Implications of stress-induced gene expression for hematopoietic stem cell aging studies

Anna Konturek-Ciesla, Rasmus Olofzon, Shabnam Kharazi & David Bryder

A decline in hematopoietic stem cell (HSC) function is believed to underlie hematological shortcomings with age; however, a comprehensive molecular understanding of these changes is currently lacking. Here we provide evidence that a transcriptional signature reported in several previous studies on HSC aging is linked to stress-induced changes in gene expression rather than aging. Our findings have strong implications for the design and interpretation of HSC aging studies.

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Hesperetin activates CISD2 to attenuate senescence in human keratinocytes from an older person and rejuvenates naturally aged skin in mice

Results

Four findings are pinpointed. **Firstly**, in human skin, CISD2 is mainly expressed in proliferating keratinocytes from the epidermal basal layer and, furthermore, CISD2 is down-regulated in the sun-exposed epidermis. **Secondly**, in HEK001 human keratinocytes from an older person, hesperetin enhances mitochondrial function and protects against reactive oxygen species-induced oxidative stress via increased CISD2 expression; this enhancement is CISD2-dependent. Additionally, hesperetin alleviates UVB-induced damage and suppresses matrix metalloproteinase-1 expression, the latter being a major indicator of UVB-induced damage in keratinocytes. **Thirdly**, transcriptomic analysis revealed that hesperetin modulates a panel of differentially expressed genes that are associated with mitochondrial function, redox homeostasis, keratinocyte function, and inflammation in order to attenuate senescence. Intriguingly, hesperetin activates two known longevity-associated regulators, namely FOXO3a and FOXM1, in order to suppress the senescence-associated secretory phenotype. **Finally**, in mouse skin, hesperetin enhances CISD2 expression to ameliorate UVB-induced photoaging and this occurs via a mechanism involving CISD2. Most strikingly, late-life treatment with hesperetin started at 21-month old and lasting for 5 months, is able to retard skin aging and rejuvenate naturally aged skin in mice.

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HDAC1/2 inhibitor therapy improves multiple organ systems in aged mice

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Aging increases the risk of age-related diseases, imposing substantial healthcare and personal costs. Targeting fundamental aging mechanisms pharmacologically can promote healthy aging and reduce this disease susceptibility. In this work, we employed transcriptome-based drug screening to identify compounds emulating transcriptional signatures of long-lived genetic interventions. We discovered compound 60 (Cmpd60), a selective histone deacetylase 1 and 2 (HDAC1/2) inhibitor, mimicking diverse longevity interventions. In extensive molecular, phenotypic, and bioinformatic assessments using various cell and aged mouse models, we found Cmpd60 treatment to improve age-related phenotypes in multiple organs. Cmpd60 reduces renal epithelial-mesenchymal transition and fibrosis in kidney, diminishes dementia-related gene expression in brain, and enhances cardiac contractility and relaxation for the heart. In sum, our two-week HDAC1/2 inhibitor treatment in aged mice establishes a multi-tissue, healthy aging intervention in mammals, holding promise for therapeutic translation to promote healthy aging in humans.

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First Optimization of Novel, Potent, Selective PDE11A4 Inhibitors for Age-Related Cognitive Decline

Shams ul Mahmood, Mariana Lozano Gonzalez, Sreedhar Tummalapalli, Jeremy Eberhard, Judy Ly, Charles S. Hoffman, Michy P. Kelly, John Gordon, Dennis Colussi, Wayne Childers, and David P. Rotella*

Phosphodiesterase 11A4 (PDE11A4) is a dual-acting cyclic nucleotide hydrolase expressed in neurons in the CA1, subiculum, amygdalostriatal transition area and amygdalohippocampal area of the extended hippocampal formation. PDE11A4 is the only PDE enzyme to emanate solely from hippocampal formation, a key brain region for the formation of long-term memory. PDE11A4 expression increases in the hippocampal formation of both humans and rodents as they age. Interestingly, PDE11A knockout mice do not show age-related deficits in associative memory and show no gross histopathology. This suggests that inhibition of PDE11A4 might serve as a therapeutic option for age-related cognitive decline. A novel, yeast-based high throughput screen previously identified moderately potent, selective PDE11A4 inhibitors, and this work describes initial efforts that improved potency more than 10-fold and improved some pharmaceutical properties of one of these scaffolds, leading to selective, cell-penetrant PDE11A4 inhibitors, one of which is 10-fold more potent compared to tadalafil in cell-based activity.

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PREPRINT

Dietary restriction of individual amino acids stimulates unique molecular responses in mouse liver

Spencer A. Haws, Yang Liu, Cara L. Green, Reji Babygirija, Eric A. Armstrong, Anusha T. Mehendale, Dudley W. Lamming, John M. Denu

Dietary protein and essential amino acid (EAA) restriction promotes favorable metabolic reprogramming, ultimately resulting in improvements to both health and lifespan. However, as individual EAAs have distinct catabolites and engage diverse downstream signaling pathways, it remains unclear to what extent shared or AA-specific molecular mechanisms promote diet-associated phenotypes. Here, we investigated the physiological and molecular effects of restricting either dietary methionine, leucine, or isoleucine (Met-R, Leu-R, and Ile-R) for 3 weeks in C57BL/6J male mice. While all 3 AA-depleted diets promoted fat and lean mass loss and slightly improved glucose tolerance, the molecular responses were more diverse; while hepatic metabolites altered by Met-R and Leu-R were highly similar, Ile-R led to dramatic changes in metabolites, including a 3-fold reduction in the oncometabolite 2-hydroxyglutarate. Pathways regulated in an EAA-specific manner included glycolysis, the pentose phosphate pathway (PPP), nucleotide metabolism, the TCA cycle and amino acid metabolism. Transcriptiome analysis and global profiling of histone post-translational modifications (PTMs) revealed different patterns of responses to each diet, although Met-R and Leu-R again shared similar transcriptional responses. While the pattern of global histone PTMs were largely unique for each dietary intervention, Met-R and Ile-R had similar changes in histone-3 methylation/acetylation PTMs at lysine-9. Few similarities were observed between the physiological or molecular responses to EAA restriction and treatment with rapamycin, an inhibitor of the mTORC1 AA-responsive protein kinase, indicating the response to EAA restriction may be largely independent of mTORC1. Together, these results demonstrate that dietary restriction of individual EAAs has unique, EAA-specific effects on the hepatic metabolome, epigenome, and transcriptome, and suggests that the specific EAAs present in dietary protein may play a key role at regulating health at the molecular level.

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Late-life shift in caloric intake affects fly metabolism and longevity

Michael Li, Jacob Macro, Kali Meadows, +6, and Blanka Rogina Authors Info & Affiliations

The prevalence of obesity is increasing in older adults and contributes to age-related decline. Caloric restriction (CR) alleviates obesity phenotypes and delays the onset of age-related changes. However, how late in life organisms benefit from switching from a high- (H) to a low-calorie (L) diet is unclear. We transferred male flies from a H to a L (HL) diet or vice versa (LH) at different times during life. Both shifts immediately change fly rate of aging even when applied late in life. HL shift rapidly reduces fly mortality rate to briefly lower rate than in flies on a constant L diet, and extends lifespan. Transcriptomic analysis uncovers that flies aged on H diet have acquired increased stress response, which may have temporal advantage over flies aged on L diet and leads to rapid decrease in mortality rate after HL switch. Conversely, a LH shift increases mortality rate, which is temporarily higher than in flies aged on a H diet, and shortens lifespan. Unexpectedly, more abundant transcriptomic changes accompanied LH shift, including increase in ribosome biogenesis, stress response and growth. These changes reflect protection from sudden release of ROS, energy storage, and use of energy to growth, which all likely contribute to higher mortality rate. As the beneficial effects of CR on physiology and lifespan are conserved across many organisms, our study provides framework to study underlying mechanisms of CR interventions that counteract the detrimental effects of H diets and reduce rate of aging even when initiated later in life.

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PREPRINT

A universal molecular mechanism driving aging

Wan Jin, Jing Zheng, Yu Xiao, Lingao Ju, Fangjin Chen, Jie Fu, Hui Jiang, Yi Zhang

How cell replication ultimately results in aging and the Hayflick limit are not fully understood. Here we show that clock-like accumulation of DNA G-quadruplexes (G4s) throughout cell replication drives conserved aging mechanisms. G4 stimulates transcription-replication interactions to delay genome replication and impairs DNA re-methylation and histone modification recovery, leading to loss of heterochromatin. This creates a more permissive local environment for G4 formation in subsequent generations. As a result, G4s gradually accumulate on promoters throughout mitosis, driving clock-like DNA hypomethylation and chromatin opening. In patients and *in vitro* models, loss-of-function mutations in the G4-resolving enzymes WRN, BLM and ERCC8 accelerate the erosion of the epigenomic landscape around G4. G4-driven epigenomic aging is strongly correlated with biological age and is conserved in yeast, nematodes, insects, fish, rodents, and humans. Our results revealed a universal molecular mechanism of aging and provided mechanistic insight into how G-quadruplex processor mutations drive premature aging.

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Nasopharyngeal lymphatic plexus is a hub for cerebrospinal fluid drainage

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Cerebrospinal fluid (CSF) in the subarachnoid space around the brain has long been known to drain through the lymphatics to cervical lymph nodes[1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17], but the connections and regulation have been challenging to identify. Here, using fluorescent CSF tracers in *Prox1-GFP* lymphatic reporter mice[18], we found that the nasopharyngeal lymphatic plexus is a major hub for CSF outflow to deep cervical lymph nodes. This plexus had unusual valves and short lymphangions but no smooth-muscle coverage, whereas downstream deep cervical lymphatics had typical semilunar valves, long lymphangions and smooth muscle coverage that transported CSF to the deep cervical lymph nodes. α-Adrenergic and nitric oxide signalling in the smooth muscle cells regulated CSF drainage through the transport properties of deep cervical lymphatics. During ageing, the nasopharyngeal lymphatic plexus atrophied, but deep cervical lymphatics were not similarly altered, and CSF outflow could still be increased by adrenergic or nitric oxide signalling. Single-cell analysis of gene expression in lymphatic endothelial cells of the nasopharyngeal plexus of aged mice revealed increased type I interferon signalling and other inflammatory cytokines. The importance of evidence for the nasopharyngeal lymphatic plexus functioning as a CSF outflow hub is highlighted by its regression during ageing. Yet, the ageing-resistant pharmacological activation of deep cervical lymphatic transport towards lymph nodes can still increase CSF outflow, offering an approach for augmenting CSF clearance in age-related neurological conditions in which greater efflux would be beneficial.

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Cell-to-cell transmitted alpha-synuclein recapitulates experimental Parkinson's disease

Parkinson's disease is characterized by a progressive accumulation of alpha-Synuclein (αSyn) neuronal inclusions called Lewy bodies in the nervous system. Lewy bodies can arise from the cell-to-cell propagation of αSyn, which can occur via sequential steps of secretion and uptake. Here, by fusing a removable short signal peptide to the N-terminus of αSyn, we developed a novel mouse model with enhanced αSyn secretion and cell-to-cell transmission. Expression of the secreted αSyn in the mouse brain was under the control of a novel hybrid promoter in combination with adeno-associated virus serotype 9 (AAV9). This combination of promoter and viral vector induced a robust expression in neurons but not in the glia of injected mice. Biochemical characterization of the secreted αSyn revealed that, in cultured cells, this protein is released to the extracellular milieu via conventional secretion. The released αSyn is then internalized and processed by acceptor cells via the endosome-lysosome pathway indicating that the secreted αSyn is cell-to-cell transmitted. The secreted αSyn is aggregation-prone and amyloidogenic, and when expressed in the brain of wild-type non-transgenic mice, it induces a Parkinson's disease-like phenotype that includes a robust αSyn pathology in the substantia nigra, neuronal loss, neuroinflammation, and motor deficits, all the key features of experimental animal models of Parkinson's disease. In summary, a novel animal model of Parkinson's disease based on enhanced cell-to-cell transmission of αSyn was developed. The neuron-produced cell-to-cell transmitted αSyn triggers all phenotypic features of experimental Parkinson's disease in mice.

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Pathological Markers of Alzheimer's Disease and Related Dementia in the Rhesus Macaque Amygdala

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PMID: 38229831 PMCID: PMC10790150 DOI: 10.3233/ADR-230184

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Abstract

Rhesus macaques develop amyloid-β (Aβ) plaques during old age, but it is unclear how extensively they express other pathological hallmarks of dementia. Here we used immunohistochemistry to examine expression of phosphorylated tau (pTau) protein and cytoplasmic inclusions of TAR DNA binding protein 43 kDa (TDP-43) within the amygdala of young and old males, and also in old surgically-menopausal females that were maintained on regular or obesogenic diets. Only one animal, a 23-year-old female, showed pTau expression and none showed TDP-43 inclusions. What genetic and/or environmental factors protect macaques from expressing more severe human neuro-pathologies remains an interesting unresolved question.

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Mucosal TLR5 activation controls healthspan and longevity

Addressing age-related immunological defects through therapeutic interventions is essential for healthy aging, as the immune system plays a crucial role in controlling infections, malignancies, and in supporting tissue homeostasis and repair. In our study, we show that stimulating toll-like receptor 5 (TLR5) via mucosal delivery of a flagellin-containing fusion protein effectively extends the lifespan and enhances the healthspan of mice of both sexes. This enhancement in healthspan is evidenced by diminished hair loss and ocular lens opacity, increased bone mineral density, improved stem cell activity, delayed thymic involution, heightened cognitive capacity, and the prevention of pulmonary lung fibrosis. Additionally, this fusion protein boosts intestinal mucosal integrity by augmenting the surface expression of TLR5 in a certain subset of dendritic cells and increasing interleukin-22 (IL-22) secretion. In this work, we present observations that underscore the benefits of TLR5-dependent stimulation in the mucosal compartment, suggesting a viable strategy for enhancing longevity and healthspan.

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PREPRINT

Epistemic uncertainty challenges aging clock reliability in predicting rejuvenation effects

Dmitrii Kriukov, Ekaterina Kuzmina, Evgeniy Efimov, Dmitry V. Dylov, Ekaterina E. Khrameeva

Epigenetic aging clocks have been widely used to validate rejuvenation effects during cellular reprogramming. However, these predictions are unverifiable because the true biological age of reprogrammed cells remains unknown. We present an analytical framework to consider rejuvenation predictions from the uncertainty perspective. Our analysis reveals that the DNA methylation profiles across reprogramming are poorly represented in the aging data used to train clock models, thus introducing high epistemic uncertainty in age estimations. Moreover, predictions of different published clocks are inconsistent, with some even suggesting zero or negative rejuvenation. While not questioning the possibility of age reversal, we show that the high clock uncertainty challenges the reliability of rejuvenation effects observed during *in vitro* reprogramming prior to pluripotency and throughout embryogenesis. Conversely, our method reveals a significant age increase after *in vivo* reprogramming. We recommend including uncertainty estimation in future aging clock models to avoid the risk of misinterpreting the results of biological age prediction.

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Prognostic accuracy of 70 individual frailty biomarkers in predicting mortality in the Canadian Longitudinal Study on Aging

The frailty index (FI) uses a deficit accumulation approach to derive a single, comprehensive, and replicable indicator of age-related health status. Yet, many researchers continue to seek a single "frailty biomarker" to facilitate clinical screening. We investigated the prognostic accuracy of 70 individual biomarkers in predicting mortality, comparing each with a composite FI. A total of 29,341 individuals from the comprehensive cohort of the Canadian Longitudinal Study on Aging were included (mean, 59.4 ± 9.9 years; 50.3% female). Twenty-three blood-based biomarkers and 47 test-based biomarkers (e.g., physical, cardiac, cardiology) were examined. Two composite FIs were derived: FI-Blood and FI-Examination. Mortality status was ascertained using provincial vital statistics linkages and contact with next of kin. Areas under the curve were calculated to compare prognostic accuracy across models (i.e., age, sex, biomarker, FI) in predicting mortality. Compared to an age-sex only model, the addition of individual biomarkers demonstrated improved model fit for 24/70 biomarkers (11 blood, 13 test-based). Inclusion of FI-Blood or FI-Examination improved mortality prediction when compared to any of the 70 biomarker-age-sex models. Individual addition of seven biomarkers (walking speed, chair rise, time up and go, pulse, red blood cell distribution width, C-reactive protein, white blood cells) demonstrated an improved fit when added to the age-sex-FI model. FI scores had better mortality risk prediction than any biomarker. Although seven biomarkers demonstrated improved prognostic accuracy when considered alongside an FI score, all biomarkers had worse prognostic accuracy on their own. Rather than a single biomarker test, implementation of routine FI assessment in clinical settings may provide a more accurate and reliable screening tool to identify those at increased risk of adverse outcomes.

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C. elegans aging research

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PREPRINT

High-content phenotypic analysis of *a C. elegans* recombinant inbred population identifies genetic and molecular regulators of lifespan

Arwen W. Gao, Gaby El Alam, Yunyun Zhu, Weisha Li, Elena Katsyuba, Jonathan Sulc, Terytty Y. Li, Xiaoxu Li, Katherine A. Overmyer, Amelia Lalou, Laurent Mouchiroud, Maroun Bou Sleiman, Matteo Cornaglia, Jean-David Morel, Riekelt H. Houtkooper, Joshua J. Coon, Johan Auwerx

Lifespan is influenced by complex interactions between genetic and environmental factors. Studying those factors in model organisms of a single genetic background limits their translational value for humans. Here, we mapped lifespan determinants in 85 genetically diverse *C. elegans* recombinant intercross advanced inbred lines (RIAILs). We assessed molecular profiles – transcriptome, proteome, and lipidome – and life-history traits, including lifespan, development, growth dynamics, and reproduction. RIAILs exhibited large variations in lifespan, which positively correlated with developmental time. Among the top candidates obtained from multi-omics data integration and QTL mapping, we validated known and novel longevity modulators, including *rict-1*, *gfm-1* and *mltn-1*. We translated their relevance to humans using UK Biobank data and showed that variants in *RICTOR* and *GFM1* are associated with an elevated risk of age-related heart disease, dementia, diabetes, kidney, and liver diseases. We organized our dataset as a resource (https://lisp-lms.shinyapps.io/RIAILs/) that allows interactive explorations for new longevity targets.

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PREPRINT

Experimental variables that impact outcomes in *Caenorhabditis elegans* aging stress response

Bradford Hull, Isabella M. Irby, Kayla M. Miller, Ally Anderson, Emily A. Gardea, George L. Sutphin

Cellular stress is a fundamental component of age-associated disease. Cells encounter various forms of stress – oxidative stress, protein misfolding, DNA damage, etc. – and respond by activating specific, well-defined stress response pathways. As we age, the burden of stress and resulting damage increases while our cells' ability to deal with the consequences becomes diminished due to dysregulation of cellular stress response pathways. Many interventions that extend lifespan activate one or more stress response pathways or allow cells to maintain normal stress response later in life. The nematode *Caenorhabditis elegans* is a commonly used model for both aging and stress response research. As such, stress response experiments are regularly conducted as part of studies focused on mechanisms of aging in *C. elegans*. However, experimental design across experiments in the field are highly variable, including stressor dose, age at exposure, culture type (liquid vs. solid), bacterial strain used as a food source, and environmental temperature. These differences can result in different experimental outcomes, making comparison of results between studies challenging. Here we evaluate several experimental variables that are variable in the published literature and find that each can meaningfully alter experimental outcomes for multiple stressors. Our goal is to raise awareness of the issue of experimental variability within the field and suggest a standardized experimental design to serve as a set of guidelines for future experiments. By adopting these guidelines as a starting point, and explicitly noting differences in specific experiments, we aim to promote rigor and reproducibility, ultimately fostering more interpretable and translatable outcomes in geroscience research.

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REVIEWS/COMMENTS/ METHODS/EDITORIALS

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Seven knowledge gaps in modern biogerontology

About a year ago, members of the editorial board of *Biogerontology* were requested to respond to a query by the editor-in-chief of the journal as to what one question within their field of ageing research still needs to be asked and answered. This editorial is inspired by the wide range and variety of questions, ideas, comments and suggestions received in response to that query. The seven knowledge gaps identified in this article are arranged into three main categories: evolutionary aspects of longevity, biological survival and death aspects, and heterogeneity in the progression and phenotype of ageing. This is not an exhaustive and exclusive list, and may be modified and expanded. Implications of these knowledge gaps, especially in the context of ongoing attempts to develop effective interventions in ageing and longevity are also discussed.

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Sex Differences in Mouse Longevity and Responses to Geroprotective Drugs: Implications for Human Intervention

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Nisi Jiang, MS, James F Nelson, PhD

The process of aging, biologically speaking, involves changes in molecular, cellular, and physiological processes over the life course of an individual that lead to losses in functional capacities, reduced resilience, decreased health, and increased vulnerability to death. Less recognized, however, are other processes such as learning and memory, which, in the absence of neurodegenerative disease, enable the accrual of experience and resilience. These and other benefits of aging have led to the important concept of the "longevity dividend" (Olshansky et al., 2007). Identifying ways both to minimize the negative and maximize the positive aspects of aging should drive policy that will benefit not only the individual but the larger community and ultimately, society at large. Here we offer some perspectives on how biological research on sex differences in aging can contribute to developing policies that better serve efforts in make lives healthier and more meaningful as we grow older.

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The hallmarks of aging as a conceptual framework for health and longevity research

 Antonio G. Tartiere[1] José M. P. Freije[1,2*] Carlos López-Otín[1,3,4]

The inexorability of the aging process has sparked the curiosity of human beings since ancient times. However, despite this interest and the extraordinary scientific advances in the field, the complexity of the process has hampered its comprehension. In this context, The Hallmarks of Aging were defined in 2013 with the aim of establishing an organized, systematic and integrative view of this topic, which would serve as a conceptual framework for aging research. Ten years later and promoted by the progress in the area, an updated version included three new hallmarks while maintaining the original scope. The aim of this review is to determine to what extent The Hallmarks of Aging achieved the purpose that gave rise to them. For this aim, we have reviewed the literature citing any of the two versions of The Hallmarks of Aging and conclude that they have served as a conceptual framework not only for aging research but also for related areas of knowledge. Finally, this review discusses the new candidates to become part of the Hallmarks list, analyzing the evidence that supports whether they should or should not be incorporated.

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Distinguishing between driver and passenger mechanisms of aging

João Pedro de Magalhães

Understanding why we age is a long-standing question, and many mechanistic theories of aging have been proposed. Owing to limitations in studying the aging process, including a lack of adequate quantitative measurements, its mechanistic basis remains a subject of debate. Here, I explore theories of aging from the perspective of causal relationships. Many aging-related changes have been observed and touted as drivers of aging, including molecular changes in the genome, telomeres, mitochondria, epigenome and proteins and cellular changes affecting stem cells, the immune system and senescent cell buildup. Determining which changes are drivers and not passengers of aging remains a challenge, however, and I discuss how animal models and human genetic studies have been used empirically to infer causality. Overall, our understanding of the drivers of human aging is still inadequate; yet with a global aging population, elucidating the causes of aging has the potential to revolutionize biomedical research.

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Hormesis determines lifespan

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This paper addresses how long lifespan can be extended via multiple interventions, such as dietary supplements [e.g., curcumin, resveratrol, sulforaphane, complex phytochemical mixtures (e.g., Moringa, Rhodiola)], pharmaceutical agents (e.g., metformin), caloric restriction, intermittent fasting, exercise and other activities. This evaluation was framed within the context of hormesis, a biphasic dose response with specific quantitative features describing the limits of biological/phenotypic plasticity for integrative biological endpoints (e.g., cell proliferation, memory, fecundity, growth, tissue repair, stem cell population expansion/differentiation, longevity). Evaluation of several hundred lifespan extending agents using yeast, nematode (Caenorhabditis elegans), multiple insect and other invertebrate and vertebrate models (e.g., fish, rodents), revealed they responded in a manner [average (mean/median) and maximum lifespans] consistent with the quantitative features [i.e., 30–60% greater at maximum (Hormesis Rule)] of the hormetic dose response. These lifespan extension features were independent of biological model, inducing agent, endpoints measured and mechanism. These findings indicate that hormesis describes the capacity to extend life via numerous agents and activities and that the magnitude of lifespan extension is modest, in the percentage, not fold, range. These findings have important implications for human aging, genetic diseases/environmental stresses and lifespan extension, as well as public health practices and long-term societal resource planning.

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Nurturing longevity through natural compounds: Where do we stand, and where do we go?

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The revolution in aging research through the past decade has driven the progress in interventions that promote longevity. Dissection of the “old” hallmarks of aging has provided solid data for the definition of at least three “new” ones, opening avenues for the development of novel hallmark-targeted pro-longevity approaches. The quest for geroprotectors is of enormous interest with the ultimate goal of finding the alchemical stone that induces healthy aging and increases lifespan, pushing the limits of human longevity or even uncovering the absence of such limits. Several of the well-appreciated geroprotectors that are recognized as longevity promoters are of natural origin such as metformin, resveratrol, aspirin, and spermidine. As the search for pharmacological modulators of healthspan and lifespan continues, numerous studies are focusing on the potential of plant secondary metabolites. The current review attempts to critically assess the available interventions and the breakthrough discoveries in the field of longevity research over the past decade. Correspondingly, novel approaches targeting the hallmarks of aging have been outlined, and the future goals in longevity research have been enlightened. Special emphasis has been placed on the potential of plant-derived compounds as pro-longevity agents.

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Anti-Aging Drugs and the Related Signal Pathways

by Nannan Du [1,2], Ruigang Yang [1,2,3], Shengrong Jiang [4], Zubiao Niu [1,2,3], Wenzhao Zhou [1,2], Chenyu Liu [1,5], Lihua Gao [1] and Qiang Sun [1,2,3,*]

Aging is a multifactorial biological process involving chronic diseases that manifest from the molecular level to the systemic level. From its inception to 31 May 2022, this study searched the PubMed, Web of Science, EBSCO, and Cochrane library databases to identify relevant research from 15,983 articles. Multiple approaches have been employed to combat aging, such as dietary restriction (DR), exercise, exchanging circulating factors, gene therapy, and anti-aging drugs. Among them, anti-aging drugs are advantageous in their ease of adherence and wide prevalence. Despite a shared functional output of aging alleviation, the current anti-aging drugs target different signal pathways that frequently cross-talk with each other. At present, six important signal pathways were identified as being critical in the aging process, including pathways for the mechanistic target of rapamycin (mTOR), AMP-activated protein kinase (AMPK), nutrient signal pathway, silent information regulator factor 2-related enzyme 1 (SIRT1), regulation of telomere length and glycogen synthase kinase-3 (GSK-3), and energy metabolism. These signal pathways could be targeted by many anti-aging drugs, with the corresponding representatives of rapamycin, metformin, acarbose, nicotinamide adenine dinucleotide (NAD^+), lithium, and nonsteroidal anti-inflammatory drugs (NSAIDs), respectively. This review summarized these important aging-related signal pathways and their representative targeting drugs in attempts to obtain insights into and promote the development of mechanism-based anti-aging strategies.

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Telomeres, cellular senescence, and aging: past and future

Over half a century has passed since Alexey Olovnikov's groundbreaking proposal of the end-replication problem in 1971, laying the foundation for our understanding of telomeres and their pivotal role in cellular senescence. This review paper delves into the intricate and multifaceted relationship between cellular senescence, the influence of telomeres in this process, and the far-reaching consequences of telomeres in the context of aging and age-related diseases. Additionally, the paper investigates the various factors that can influence telomere shortening beyond the confines of the end-replication problem and how telomeres can exert their impact on aging, even in the absence of significant shortening. Ultimately, this paper stands as a tribute to the pioneering work of Olovnikov, whose seminal contributions established the solid foundation upon which our ongoing explorations of telomeres and the aging process are based.

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The Impact of Apolipoprotein E (*APOE*) Epigenetics on Aging and Sporadic Alzheimer's Disease

by Madia Lozupone [1,*], Vittorio Dibello [2], Rodolfo Sardone [3], Fabio Castellana [4], Roberta Zupo [4], Luisa Lampignano [5], Ilaria Bortone [1], Antonio Daniele [6,7], Antonello Bellomo [8], Vincenzo Solfrizzi [4] and Francesco Panza [4,*]

Sporadic Alzheimer's disease (AD) derives from an interplay among environmental factors and genetic variants, while epigenetic modifications have been expected to affect the onset and progression of its complex etiopathology. Carriers of one copy of the apolipoprotein E gene (*APOE*) *ε4* allele have a 4-fold increased AD risk, while *APOE ε4/ε4*-carriers have a 12-fold increased risk of developing AD in comparison with the *APOE ε3*-carriers. The main longevity factor is the homozygous *APOE* ε3/ε3 genotype. In the present narrative review article, we summarized and described the role of *APOE* epigenetics in aging and AD pathophysiology. It is not fully understood how *APOE* variants may increase or decrease AD risk, but this gene may affect tau- and amyloid-mediated neurodegeneration directly or indirectly, also by affecting lipid metabolism and inflammation. For sporadic AD, epigenetic regulatory mechanisms may control and influence *APOE* expression in response to external insults. Diet, a major environmental factor, has been significantly associated with physical exercise, cognitive function, and the methylation level of several cytosine-phosphate-guanine (CpG) dinucleotide sites of *APOE*.

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Non-Intrinsic, Systemic Mechanisms of Cellular Senescence

by Rachael E. Schwartz and Irina M. Conboy *

Cellular senescence is believed to contribute to aging and disease through the activity of secreted factors that promote inflammation, remodel the extracellular matrix, and adversely modify the behavior of non-senescent cells. While the markers and properties of senescent cells are still under investigation, it is postulated that cellular senescence manifests in vivo as the consequence of cellular damage that accumulates and becomes exacerbated with time. Yet, the notions that senescence has a solely intrinsic and time-dependent nature are questioned by the rapid induction of senescence in young mice and young cells in vitro by exposure to blood from aged animals. Here, we review some of the research on the systemically present factors that increase with age and may contribute to extrinsically induced senescence or "bystander senescence". These include proteins, reactive oxygen species, lipids, and nucleic acids, which may be present in individual soluble form, in vesicles, and in non-membranous multi-component macromolecules.

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Age-Related Alternative Splicing: Driver or Passenger in the Aging Process?

by Marco Baralle [1] and Maurizio Romano [2,*]

Alternative splicing changes are closely linked to aging, though it remains unclear if they are drivers or effects. As organisms age, splicing patterns change, varying gene isoform levels and functions. These changes may contribute to aging alterations rather than just reflect declining RNA quality control. Three main splicing types—intron retention, cassette exons, and cryptic exons—play key roles in age-related complexity. These events modify protein domains and increase nonsense-mediated decay, shifting protein isoform levels and functions. This may potentially drive aging or serve as a biomarker. Fluctuations in splicing factor expression also occur with aging. Somatic mutations in splicing genes can also promote aging and age-related disease. The interplay between splicing and aging has major implications for aging biology, though differentiating correlation and causation remains challenging. Declaring a splicing factor or event as a driver requires comprehensive evaluation of the associated molecular and physiological changes. A greater understanding of how RNA splicing machinery and downstream targets are impacted by aging is essential to conclusively establish the role of splicing in driving aging, representing a promising area with key implications for understanding aging, developing novel therapeutical options, and ultimately leading to an increase in the healthy human lifespan.

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A comprehensive clinically informed map of dependencies in cancer cells and framework for target prioritization

Clare Pacini • Emma Duncan • Emanuel Gonçalves • ... Leopold Parts • Francesco Iorio • Mathew J. Garnett [9] • Show all authors • Show footnotes

Genetic screens in cancer cell lines inform gene function and drug discovery. More comprehensive screen datasets with multi-omics data are needed to enhance opportunities to functionally map genetic vulnerabilities. Here, we construct a second-generation map of cancer dependencies by annotating 930 cancer cell lines with multi-omic data and analyze relationships between molecular markers and cancer dependencies derived from CRISPR-Cas9 screens. We identify dependency-associated gene expression markers beyond driver genes, and observe many gene addiction relationships driven by gain of function rather than synthetic lethal effects. By combining clinically informed dependency-marker associations with protein-protein interaction networks, we identify 370 anti-cancer priority targets for 27 cancer types, many of which have network-based evidence of a functional link with a marker in a cancer type. Mapping these targets to sequenced tumor cohorts identifies tractable targets in different cancer types. This target prioritization map enhances understanding of gene dependencies and identifies candidate anti-cancer targets for drug development.

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