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Scientific News
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Sven Bulterijs

Business/Conferences/ General news

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De Morgen
18 April at 10:19 ·

Zelfs wie na 30 jaar roken plots stopt, boekt onmiddellijk gezondheidswinst.

DEMORGEN.BE

Na je laatste sigaret herleeft je lichaam metéén: 'Wie stopt, wordt gemiddeld tien jaar ouder'

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I am cited in this newspaper article that critically looks at the claim from US researchers that the trend for increased cancer incidence in younger people is due to accelerated aging.

NIEUWSBLAD.BE

Amerikaanse onderzoekers suggereren nieuwe verklaring voor stijgend aantal kankers bij jonge mensen, maar Vlaamse artsen geloven er niet in: "Onmogelijk"

I will attend

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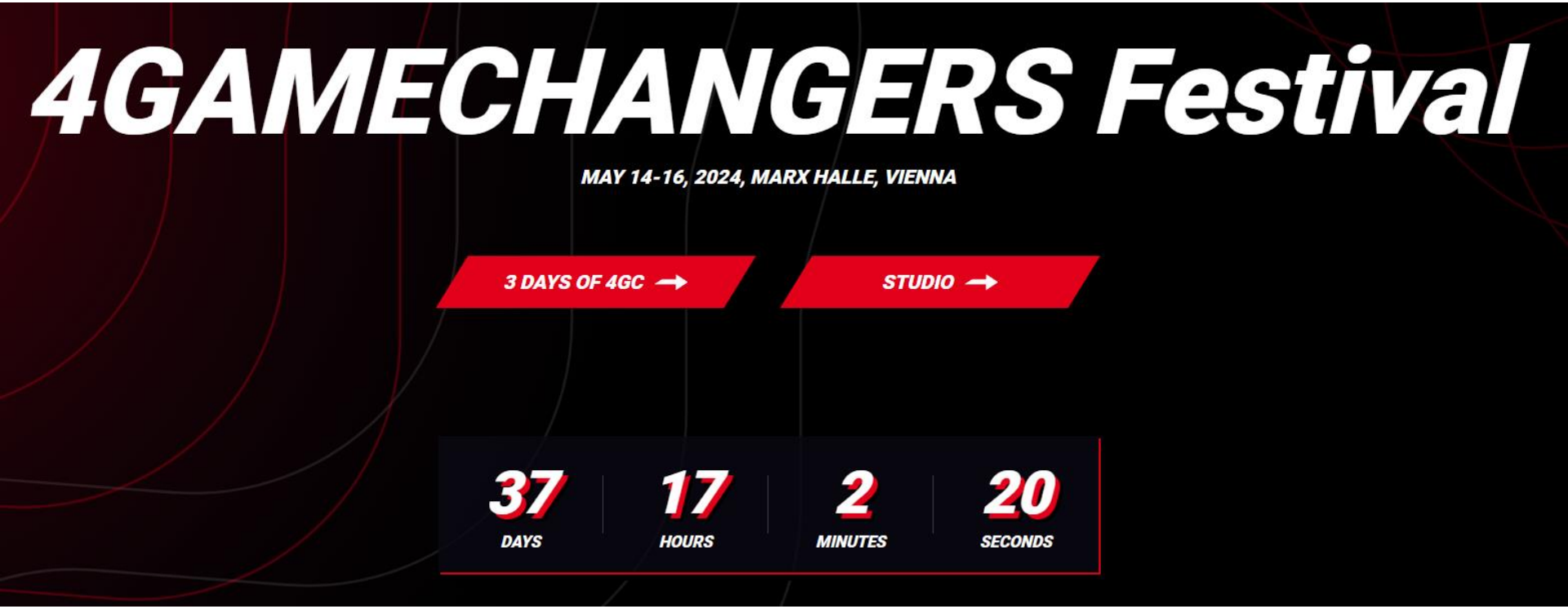
I will be in a panel on aging



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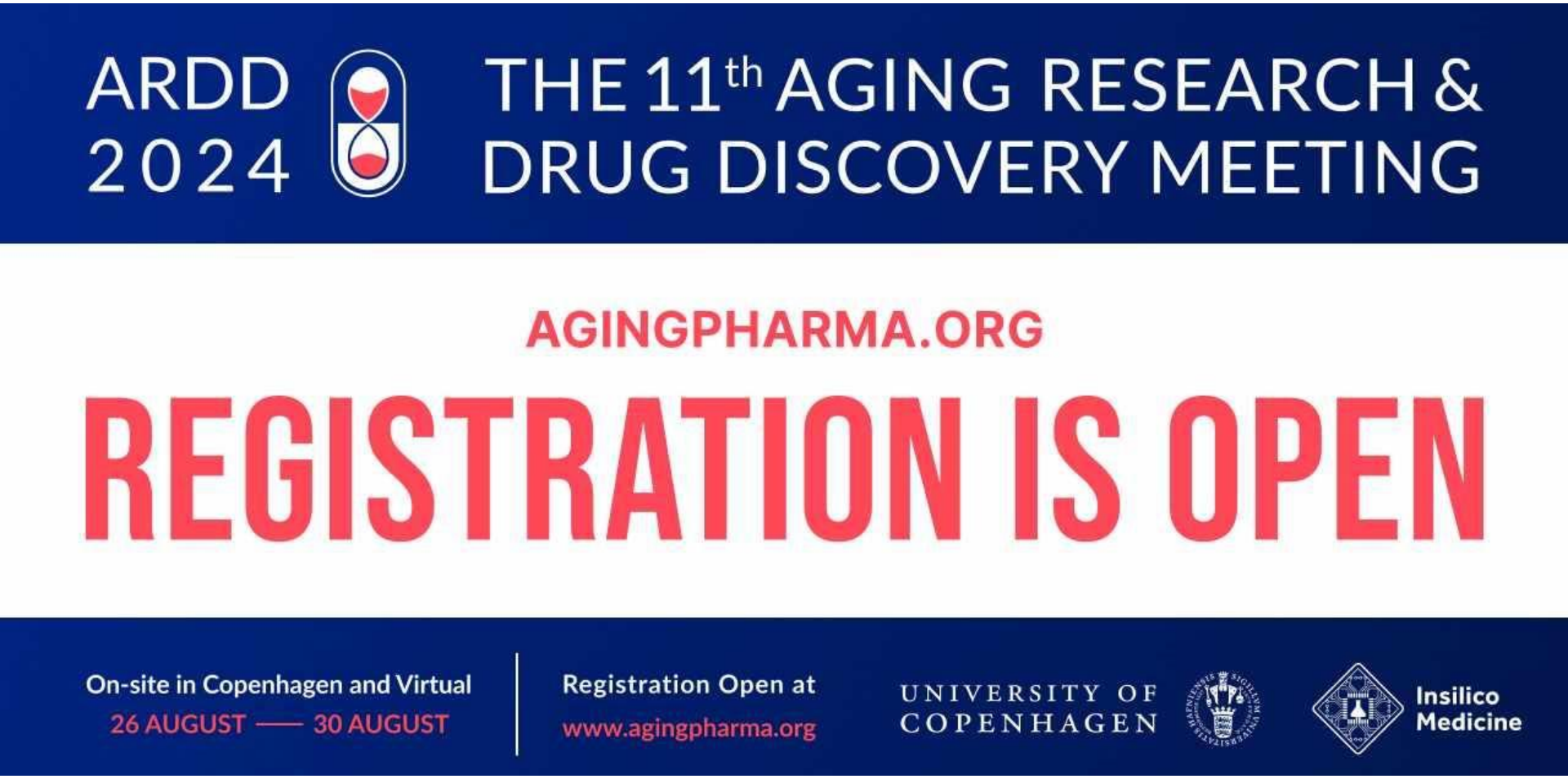

Aging research articles

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Young Plasma Rejuvenates Blood DNA Methylation Profile, Extends Mean Lifespan, and Improves Physical Appearance in Old Rats

There is converging evidence that young blood conveys cells, vesicles, and molecules able to revitalize function and restore organ integrity in old individuals. We assessed the effects of young plasma on the lifespan, epigenetic age, and healthspan of old female rats. Beginning at 25.6 months of age, a group of 9 rats (group T) was intraperitoneally injected with plasma from young rats until their natural death. A group of 8 control rats of the same age received no treatment (group C). Blood samples were collected every other week. Survival curves showed that from age 26 to 30 months, none of the group T animals died, whereas the survival curve of group C rats began to decline at age 26 months. Blood DNAm age versus chronological age showed that DNAm age in young animals increased faster than chronological age, then slowed down, entering a plateau after 27 months. The DNAm age of the treated rats fell below the DNAm age of controls and, in numerical terms, remained consistently lower until natural death. When rats were grouped according to the similarities in their differential blood DNA methylation profile, samples from the treated and control rats clustered in separate groups. Analysis of promoter differential methylation in genes involved in systemic regulatory activities revealed specific GO term enrichment related to the insulin-like factors pathways as well as to cytokines and chemokines associated with immune and homeostatic functions. We conclude that young plasma therapy may constitute a natural, noninvasive intervention for epigenetic rejuvenation and health enhancement.

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Small extracellular vesicles from young plasma reverse age-related functional declines by improving mitochondrial energy metabolism

Recent investigations into heterochronic parabiosis have unveiled robust rejuvenating effects of young blood on aged tissues. However, the specific rejuvenating mechanisms remain incompletely elucidated. Here we demonstrate that small extracellular vesicles (sEVs) from the plasma of young mice counteract pre-existing aging at molecular, mitochondrial, cellular and physiological levels. Intravenous injection of young sEVs into aged mice extends their lifespan, mitigates senescent phenotypes and ameliorates age-associated functional declines in multiple tissues. Quantitative proteomic analyses identified substantial alterations in the proteomes of aged tissues after young sEV treatment, and these changes are closely associated with metabolic processes. Mechanistic investigations reveal that young sEVs stimulate PGC-1α expression in vitro and in vivo through their miRNA cargoes, thereby improving mitochondrial functions and mitigating mitochondrial deficits in aged tissues. Overall, this study demonstrates that young sEVs reverse degenerative changes and age-related dysfunction, at least in part, by stimulating PGC-1α expression and enhancing mitochondrial energy metabolism.

PD1 blockade improves survival and CD8$^+$ cytotoxic capacity, without increasing inflammation, during normal microbial experience in old mice

By 2030, individuals 65 years of age or older will make up approximately 20% of the world's population[1]. Older individuals are at the highest risk for mortality from infections, largely due to the pro-inflammatory, dysfunctional immune response, which is collectively known as immunosenescence[2]. During aging, CD8$^+$ T cells acquire an exhausted phenotype, including increased expression of inhibitory receptors, such as programmed cell death 1 (PD1), a decline in effector function and elevated expression of inflammatory factors[3-7]. PD1 reduces T cell receptor activity via SHP2-dependent dephosphorylation of multiple pathways; accordingly, inhibiting PD1 activity through monoclonal antibodies increases CD8$^+$ T cell effector response in young mice[8-11]. Attempts to improve CD8$^+$ T cell responses by blocking inhibitory receptors are attractive; however, they can lead to adverse immune events due to overamplification of T cell receptor signaling and T cell activation[12,13]. Here we investigated the effect of monoclonal anti-PD1 immunotherapy during normal microbial experience, otherwise known as exposure to dirty mice, to determine whether it either improves exhausted CD8$^+$ T cell responses in old mice or leads to a heightened inflammatory response and increased mortality.

Evolution of T cells in the cancer-resistant naked mole-rat

Tzuhua D. Lin, Nimrod D. Rubinstein ✉, Nicole L. Fong, Megan Smith, Wendy Craft, Baby Martin-McNulty, Rebecca Perry, Martha A. Delaney, Margaret A. Roy & Rochelle Buffenstein ✉

Naked mole-rats (NMRs) are best known for their extreme longevity and cancer resistance, suggesting that their immune system might have evolved to facilitate these phenotypes. Natural killer (NK) and T cells have evolved to detect and destroy cells infected with pathogens and to provide an early response to malignancies. While it is known that NMRs lack NK cells, likely lost during evolution, little is known about their T-cell subsets in terms of the evolution of the genes that regulate their function, their clonotypic diversity, and the thymus where they mature. Here we find, using single-cell transcriptomics, that NMRs have a large circulating population of γδT cells, which in mice and humans mostly reside in peripheral tissues and induce anti-cancer cytotoxicity. Using single-cell-T-cell-receptor sequencing, we find that a cytotoxic γδT-cell subset of NMRs harbors a dominant clonotype, and that their conventional CD8 αβT cells exhibit modest clonotypic diversity. Consistently, perinatal NMR thymuses are considerably smaller than those of mice yet follow similar involution progression. Our findings suggest that NMRs have evolved under a relaxed intracellular pathogenic selective pressure that may have allowed cancer resistance and longevity to become stronger targets of selection to which the immune system has responded by utilizing γδT cells.

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Multi-omics characterization of partial chemical reprogramming reveals evidence of cell rejuvenation

Wayne Mitchell, Ludger JE Goeminne, Alexander Tyshkovskiy, Sirui Zhang, Julie Y Chen, Joao A Paulo, Kerry A Pierce, Angelina H Choy, Clary B Clish ... Vadim N Gladyshev see all »

Partial reprogramming by cyclic short-term expression of Yamanaka factors holds promise for shifting cells to younger states and consequently delaying the onset of many diseases of aging. However, the delivery of transgenes and potential risk of teratoma formation present challenges for in vivo applications. Recent advances include the use of cocktails of compounds to reprogram somatic cells, but the characteristics and mechanisms of partial cellular reprogramming by chemicals remain unclear. Here, we report a multi-omics characterization of partial chemical reprogramming in fibroblasts from young and aged mice. We measured the effects of partial chemical reprogramming on the epigenome, transcriptome, proteome, phosphoproteome, and metabolome. At the transcriptome, proteome, and phosphoproteome levels, we saw widescale changes induced by this treatment, with the most notable signature being an upregulation of mitochondrial oxidative phosphorylation. Furthermore, at the metabolome level, we observed a reduction in the accumulation of aging-related metabolites. Using both transcriptomic and epigenetic clock-based analyses, we show that partial chemical reprogramming reduces the biological age of mouse fibroblasts. We demonstrate that these changes have functional impacts, as evidenced by changes in cellular respiration and mitochondrial membrane potential. Taken together, these results illuminate the potential for chemical reprogramming reagents to rejuvenate aged biological systems and warrant further investigation into adapting these approaches for in vivo age reversal.

Pregnancy is linked to faster epigenetic aging in young women

Calen P. Ryan, Nanette R. Lee, Delia B. Carba, +5, and Christopher W. Kuzawa Authors Info & Affiliations

A central prediction of evolutionary theory is that energy invested into reproduction comes at the expense of somatic maintenance and repair, accelerating biological aging. Supporting this prediction are findings that high fertility among women predicts shorter lifespan and poorer health later in life. However, biological aging is thought to begin before age-related health declines, limiting the applicability of morbidity and mortality for studying the aging process earlier in life. Here, we examine the relationship between reproductive history and biological aging in a sample of young (20 to 22yo) men and women from the Cebu Longitudinal Health and Nutrition Survey, located in the Philippines (n = 1,735). We quantify biological aging using six measures, collectively known as epigenetic clocks, reflecting various facets of cellular aging, health, and mortality risk. In a subset of women, we test whether longitudinal changes in gravidity between young and early–middle adulthood (25 to 31yo) are associated with changes in epigenetic aging during that time. Cross-sectionally, gravidity was associated with all six measures of accelerated epigenetic aging in women (n = 825). Furthermore, longitudinal increases in gravidity were linked to accelerated epigenetic aging in two epigenetic clocks (n = 331). In contrast, the number of pregnancies a man reported fathering was not associated with epigenetic aging among same-aged cohort men (n = 910). These effects were robust to socioecological, environmental, and immunological factors, consistent with the hypothesis that pregnancy accelerates biological aging and that these effects can be detected in young women in a high-fertility context.

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Genetic predisposition, modifiable lifestyles, and their joint effects on human lifespan: evidence from multiple cohort studies FREE

Participants 353 742 adults of European ancestry, who were recruited from 2006 to 2010 and were followed up until 2021.

Exposures A polygenic risk score for lifespan with long (<lowest quintile), intermediate (quintiles 2 to 4), and short (>highest quintile) risk categories and a weighted healthy lifestyle score, including no current smoking, moderate alcohol consumption, regular physical activity, healthy body shape, adequate sleep duration, and a healthy diet, categorised into favourable, intermediate, and unfavourable lifestyles.

Main outcome measures Lifespan defined as the date of death or the censor date minus the date of birth.

Results Of the included 353 742 participants of European ancestry with a median follow-up of 12.86 years, 24 239 death cases were identified. Participants were grouped into three genetically determined lifespan categories including long (20.1%), intermediate (60.1%), and short (19.8%), and into three lifestyle score categories including favourable (23.1%), intermediate (55.6%), and unfavourable (21.3%). The hazard ratio (HR) of death for individuals with a genetic predisposition to a short lifespan was 1.21 (95% CI 1.16 to 1.26) compared to those with a genetic predisposition to a long lifespan. The HR of death for individuals in the unfavourable lifestyle category was 1.78 (95% CI 1.71 to 1.85), compared with those in the favourable lifestyle category. Participants with a genetic predisposition to a short lifespan and an unfavourable lifestyle had 2.04 times (95% CI 1.87 to 2.22) higher rates of death compared with those with a genetic predisposition to a long lifespan and a favourable lifestyle. No multiplicative interaction was detected between the polygenic risk score of lifespan and the weighted healthy lifestyle score (p=0.10). The optimal combination of healthy lifestyles, including never smoking, regular physical activity, adequate sleep duration, and a healthy diet, was derived to decrease risk of premature death (death before 75 years).

Conclusion Genetic and lifestyle factors were independently associated with lifespan. Adherence to healthy lifestyles could largely attenuate the genetic risk of a shorter lifespan or premature death. The optimal combination of healthy lifestyles could convey better benefits for a longer lifespan, regardless of genetic background.

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PREPRINT

Metabolite accumulation from oral NMN supplementation drives aging-specific kidney inflammation

Tara A. Saleh, Jeremy Whitson, Phoebe Keiser, Praveena Prasad, Brenita C. Jenkins, Tori Sodeinde, Carolyn N. Mann, Peter S. Rabinovitch, Melanie R. McReynolds, Mariya T. Sweetwyne

The mitochondrial-rich renal tubule cells are key regulators of blood homeostasis via excretion and reabsorption of metabolic waste. With age, tubules are subject to increasing mitochondrial dysfunction and declining nicotinamide adenine dinucleotide (NAD^+) levels, both hampering ATP production efficiency. We tested two mitochondrial interventions in young (6-mo) and aged (26-mo) adult male mice: elamipretide (ELAM), a tetrapeptide in clinical trials that improves mitochondrial structure and function, and nicotinamide mononucleotide (NMN), an NAD^+ intermediate and commercially available oral supplement. Kidneys were analyzed from young and aged mice after eight weeks of treatment with ELAM (3 mg/kg/day), NMN (300 mg/kg/day), or from aged mice treated with the two interventions combined (ELAM+NMN). We hypothesized that combining pharmacologic treatments to ameliorate mitochondrial dysfunction and boost NAD^+ levels, would more effectively reduce kidney aging than either intervention alone. Unexpectedly, in aged kidneys, NMN increased expression of genetic markers of inflammation (IL-1β and Ccl2) and tubule injury (Kim-1). Metabolomics of endpoint sera showed that NMN-treated aged mice had higher circulating levels of uremic toxins than either aged controls or young NMN-treated mice. ELAM+NMN-treated aged mice accumulated uremic toxins like NMN-only aged mice, but reduced IL-1β and Ccl2 kidney mRNA. This suggests that pre-existing mitochondrial dysfunction in aged kidney underlies susceptibility to inflammatory signaling with NMN supplementation in aged, but not young, mice. These findings demonstrate age and tissue dependent effects on downstream metabolic accumulation from NMN and highlight the need for targeted analysis of aged kidneys to assess the safety of anti-aging supplements in older populations.

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Neuronal cell cycle reentry events in the aging brain are more prevalent in neurodegeneration and lead to cellular senescence

Deng Wu, Jacquelyne Ka-Li Sun, Kim Hei-Man Chow

Increasing evidence indicates that terminally differentiated neurons in the brain may recommit to a cell cycle-like process during neuronal aging and under disease conditions. Because of the rare existence and random localization of these cells in the brain, their molecular profiles and disease-specific heterogeneities remain unclear. Through a bioinformatics approach that allows integrated analyses of multiple single-nucleus transcriptome datasets from human brain samples, these rare cell populations were identified and selected for further characterization. Our analyses indicated that these cell cycle-related events occur predominantly in excitatory neurons and that cellular senescence is likely their immediate terminal fate. Quantitatively, the number of cell cycle re-engaging and senescent neurons decreased during the normal brain aging process, but in the context of late-onset Alzheimer's disease (AD), these cells accumulate instead. Transcriptomic profiling of these cells suggested that disease-specific differences were predominantly tied to the early stage of the senescence process, revealing that these cells presented more proinflammatory, metabolically deregulated, and pathology-associated signatures in disease-affected brains. Similarly, these general features of cell cycle re-engaging neurons were also observed in a subpopulation of dopaminergic neurons identified in the Parkinson's disease (PD)-Lewy body dementia (LBD) model. An extended analysis conducted in a mouse model of brain aging further validated the ability of this bioinformatics approach to determine the robust relationship between the cell cycle and senescence processes in neurons in this cross-species setting.

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Aβ oligomers peak in early stages of Alzheimer's disease preceding tau pathology

Introduction: Soluble amyloid beta (Aβ) oligomers have been suggested as initiating Aβ related neuropathologic change in Alzheimer's disease (AD) but their quantitative distribution and chronological sequence within the AD continuum remain unclear.

Methods: A total of 526 participants in early clinical stages of AD and controls from a longitudinal cohort were neurobiologically classified for amyloid and tau pathology applying the AT(N) system. Aβ and tau oligomers in the quantified cerebrospinal fluid (CSF) were measured using surface-based fluorescence intensity distribution analysis (sFIDA) technology.

Results: Across groups, highest Aβ oligomer levels were found in A+ with subjective cognitive decline and mild cognitive impairment. Aβ oligomers were significantly higher in A+T- compared to A-T- and A+T+. *APOE ε*4 allele carriers showed significantly higher Aβ oligomer levels. No differences in tau oligomers were detected.

Discussion: The accumulation of Aβ oligomers in the CSF peaks early within the AD continuum, preceding tau pathology. Disease-modifying treatments targeting Aβ oligomers might have the highest therapeutic effect in these disease stages.

Highlights: Using surface-based fluorescence intensity distribution analysis (sFIDA) technology, we quantified Aβ oligomers in cerebrospinal fluid (CSF) samples of the DZNE-Longitudinal Cognitive Impairment and Dementia (DELCODE) cohortAβ oligomers were significantly elevated in mild cognitive impairment (MCI)Amyloid-positive subjects in the subjective cognitive decline (SCD) group increased compared to the amyloid-negative control groupInterestingly, levels of Aβ oligomers decrease at advanced stages of the disease (A+T+), which might be explained by altered clearing mechanisms.

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PREPRINT

A systems-biology approach connects aging mechanisms with Alzheimer's disease pathogenesis

Matthew J Leventhal, Camila A Zanella, Byunguk Kang, Jiajie Peng, David Gritsch, Zhixiang Liao, Hassan Bukhari, Tao Wang, Ping-Chieh Pao, Serwah Danquah, Joseph Benetatos, Ralda Nehme, Samouil Farhi, Li-Huei Tsai, Xianjun Dong, Clemens R Scherzer, Mel B Feany, Ernest Fraenkel

Age is the strongest risk factor for developing Alzheimer's disease, the most common neurodegenerative disorder. However, the mechanisms connecting advancing age to neurodegeneration in Alzheimer's disease are incompletely understood. We conducted an unbiased, genome-scale, forward genetic screen for age-associated neurodegeneration in *Drosophila* to identify the underlying biological processes required for maintenance of aging neurons. To connect genetic screen hits to Alzheimer's disease pathways, we measured proteomics, phosphoproteomics, and metabolomics in *Drosophila* models of Alzheimer's disease. We further identified Alzheimer's disease human genetic variants that modify expression in disease-vulnerable neurons. Through multi-omic, multi-species network integration of these data, we identified relationships between screen hits and tau-mediated neurotoxicity. Furthermore, we computationally and experimentally identified relationships between screen hits and DNA damage in *Drosophila* and human iPSC-derived neural progenitor cells. Our work identifies candidate pathways that could be targeted to attenuate the effects of age on neurodegeneration and Alzheimer's disease.

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Accumulation of APP C-terminal fragments causes endolysosomal dysfunction through the dysregulation of late endosome to lysosome-ER contact sites

Marine Bretou • Ragna Sannerud • Abril Escamilla-Ayala • ... Keimpe Wierda • Eeva-Liisa Eskelinen • Wim Annaert [7] • Show all authors • Show footnotes

Neuronal endosomal and lysosomal abnormalities are among the early changes observed in Alzheimer's disease (AD) before plaques appear. However, it is unclear whether distinct endolysosomal defects are temporally organized and how altered γ-secretase function or amyloid precursor protein (APP) metabolism contribute to these changes. Inhibiting γ-secretase chronically, in mouse embryonic fibroblast and hippocampal neurons, led to a gradual endolysosomal collapse initiated by decreased lysosomal calcium and increased cholesterol, causing downstream defects in endosomal recycling and maturation. This endolysosomal demise is γ-secretase dependent, requires membrane-tethered APP cytoplasmic domains, and is rescued by APP depletion. APP C-terminal fragments (CTFs) localized to late endosome/lysosome-endoplasmic reticulum contacts; an excess of APP-CTFs herein reduced lysosomal Ca^{2+} refilling from the endoplasmic reticulum, promoting cholesterol accretion. Tonic regulation by APP-CTFs provides a mechanistic explanation for their cellular toxicity: failure to timely degrade APP-CTFs sustains downstream signaling, instigating lysosomal dyshomeostasis, as observed in prodromal AD. This is the opposite of substrates such as Notch, which require intramembrane proteolysis to initiate signaling.

Molecular mechanisms implicated in protein changes in the Alzheimer's disease human hippocampus

Hai Duc Nguyen [1], Woong-Ki Kim [2], Huong Huong Vu [3]

This study aimed to elucidate the specific biochemical pathways linked to changes in proteins in the Alzheimer's disease (AD) human hippocampus. Our data demonstrate a constant rise in the expression of four proteins (VGF, GFAP, HSPB1, and APP) across all eleven studies. Notably, UBC was the most centrally involved and had increased expression in the hippocampus tissue of individuals with AD. Modified proteins in the hippocampal tissue were found to activate the innate immune system and disrupt communication across chemical synapses. Four hub proteins (CD44, APP, ITGB2, and APOE) are connected to amyloid plaques, whereas two hub proteins (RPL24 and RPS23) are related to neurofibrillary tangles (NFTs). The presence of modified proteins was discovered to trigger the activation of microglia and decrease the functioning of ribosomes and mitochondria in the hippocampus. Three significant microRNAs (hsa-miR-106b-5p, hsa-miR-17-5p, and hsa-miR-16-5p) and transcription factors (MYT1L, PIN1, and CSRNP3) have been discovered to improve our understanding of the alterations in proteins within the hippocampal tissues that lead to the progression of AD. These findings establish a path for possible treatments for AD to employ therapeutic strategies that specifically focus on the proteins or processes linked to the illness.

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Clinical evidence of hyperbaric oxygen therapy for Alzheimer's disease: a systematic review and meta-analysis of randomized controlled trials

Guangyao Lin [1], Li Zhao [1], Jingyu Lin [1], Xuanling Li [1], Lianwei Xu [1]

Objective: To evaluate the potential benefits of hyperbaric oxygen intervention on people with Alzheimer's disease (AD) based on the existing randomized controlled trials (RCTs).

Methods: A systematic search was conducted in nine databases until November 17, 2023, for RCTs assessing the effect of hyperbaric oxygen intervention for AD. The primary outcomes included Mini-Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog), activities of daily living (ADL), and adverse events. All results were shown in forest plots, and sensitivity analysis was adopted to further verify the robustness of the pooled results.

Results: A total of 11 RCTs recruiting 847 participants were included in this meta-analysis. Based on the pooled evidence, hyperbaric oxygen could remarkably ameliorate MMSE [MD = 3.08, 95%CI (2.56, 3.61), $p < 0.00001$], ADAS-Cog [MD = -4.53, 95%CI (-5.05, -4.00), $p < 0.00001$], ADL [MD = 10.12, 95%CI (4.46, 15.79), $p = 0.0005$], MDA levels [SMD = -2.83, 95%CI (-5.27, -0.38), $p = 0.02$], SOD levels [SMD = 2.12, 95%CI (1.10, 3.15), $p < 0.0001$], IL-1-β levels [SMD = -1.00, 95%CI (-1.48, -0.53), $p < 0.0001$], and TGF-β1 levels [MD = 4.87, 95%CI (3.98, 5.76), $p < 0.00001$] without adverse events [OR = 1.17, 95%CI (0.68, 2.03), $p = 0.58$] for people with AD. The pooled results were robust after checking by sensitivity analysis.

Conclusion: These evidences suggest that hyperbaric oxygen is an effective and safe intervention for the treatment of AD. Further studies with more rigorous design will help to fully evaluate the clinical value of hyperbaric oxygen on cognition function in people with AD.

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Cognitively healthy centenarians are genetically protected against Alzheimer's disease

Niccolo' Tesi [1 2 3], Sven van der Lee [2 3], Marc Hulsman [1 2 3], Natasja M van Schoor [4 5], Martijn Huisman [4 5], Yolande Pijnenburg [3], Wiesje M van der Flier [3 4], Marcel Reinders [1], Henne Holstege [1 2 3]

Background: Alzheimer's disease (AD) prevalence increases with age, yet a small fraction of the population reaches ages > 100 years without cognitive decline. We studied the genetic factors associated with such resilience against AD.

Methods: Genome-wide association studies identified 86 single nucleotide polymorphisms (SNPs) associated with AD risk. We estimated SNP frequency in 2281 AD cases, 3165 age-matched controls, and 346 cognitively healthy centenarians. We calculated a polygenic risk score (PRS) for each individual and investigated the functional properties of SNPs enriched/depleted in centenarians.

Results: Cognitively healthy centenarians were enriched with the protective alleles of the SNPs associated with AD risk. The protective effect concentrated on the alleles in/near ANKH, GRN, TMEM106B, SORT1, PLCG2, RIN3, and APOE genes. This translated to >5-fold lower PRS in centenarians compared to AD cases ($P = 7.69 \times 10^{-71}$), and 2-fold lower compared to age-matched controls ($P = 5.83 \times 10^{-17}$).

Discussion: Maintaining cognitive health until extreme ages requires complex genetic protection against AD, which concentrates on the genes associated with the endolysosomal and immune systems.

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PREPRINT

Genetic determinants of centenarian longevity, as quantified by the 'CentPGS' score, are associated with a lower risk of multiple age-related diseases and a longer healthspan.

Centenarians exhibit remarkable longevity, and exploring the genetic determinants of that longevity is crucial for understanding the mechanisms of human ageing. Although APOE4 is the most common implicated negative factor in longevity, other genetic factors and their associated phenotypes are not fully understood. We conducted a genome-wide association study (GWAS) of 964 Japanese centenarians (including 173 supercentenarians) and 7,306 controls to identify the genetic components of longevity and the correlated phenotypes. GWAS summary statistics revealed that the genetic components of longevity were negatively associated with the risk of multiple age-related diseases and biometrics. Survival analysis indicated that a polygenic score derived from these summary statistics, called CentPGS, was correlated with healthspan in a cohort of healthy older people. This association was independent of APOE4 genotype and sex, suggesting that CentPGS is a promising genetic indicator of healthspan and may be used in future investigations into healthy longevity.

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Normal or improved cardiovascular risk factors in IGF-I-deficient adults with growth hormone receptor deficiency

Jaime Guevara-Aguirre [10] • Amrendra Mishra [10] • Marco Canepa • ... John J. Kopchick • Priya Balasubramanian • Valter D. Longo [11] • Show all authors • Show footnotes

Background

Human subjects with generalized growth hormone (GH) insensitivity due to GH receptor deficiency (GHRD)/Laron syndrome display a very low incidence of insulin resistance, diabetes, and cancer, as well as delayed age-related cognitive decline. However, the risk of cardiovascular disease (CVD) in these subjects is poorly understood. Here, we have assessed cardiovascular function, damage, and risk factors in GHRD subjects and their relatives.

Methods

We measured markers of CVD in two phases: one in a cohort of 30 individuals (GHRD = 16, control relatives = 14) brought to USC (in Los Angeles, CA) and one in a cohort including additional individuals examined in Ecuador (where the subjects live) for a total of 44 individuals (GHRD = 21, control relatives = 23). Data were collected on GHRD and control groups living in similar geographical locations and sharing comparable environmental and socio-economic circumstances.

Results

Compared to controls, GHRD subjects displayed lower serum glucose, insulin, blood pressure, smaller cardiac dimensions, similar pulse wave velocity, lower carotid artery intima-media thickness, lower creatinine, and a non-significant but major reduction in the portion of subjects with carotid atherosclerotic plaques (7% GHRDs vs. 36%, Controls $p = 0.1333$) despite elevated low-density lipoprotein cholesterol levels.

Conclusion

The current study indicates that individuals with GHRD have normal or improved levels of cardiovascular disease risk factors as compared to their relatives.

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PREPRINT

Deciphering the Timing and Impact of Life-extending Drugs: A Novel Analytic Approach that Differentiates Early, Midlife, and Senescence Phase Efficacies

Nisi Jiang, Catherine J. Cheng, Qianqian Liu, Randy Strong, Jonathan Gelfond, James F. Nelson

Evidence that life-extending interventions are not uniformly effective across the lifespan calls for an analytic tool that can estimate age-specific treatment effects on mortality hazards. Here we report such a tool, applying it to mouse data from 42 agents tested in the NIA Interventions Testing Program. This tool identified agents that either reduced (22) or increased (16) mortality hazards or did both (6), all with marked variation in the duration of efficacy and magnitude of effect size. Only 7 reduced mortality hazards after the 90% mortality, when the burden of senescence is greatest. Sex differences were apparent in all parameters. This new analytic tool complements the commonly used log-rank test. It detects more potential life-extending candidates (22 versus 10) and indicates when during the life course they are effective. It also uncovers adverse effects. Most importantly, it identifies agents that specifically reduce mortality hazards during the senescent phase of life.

Identification of prospective aging drug targets via Mendelian randomization analysis

Rui Mao, Ji Li, Wenqin Xiao

Aging represents a multifaceted process culminating in the deterioration of biological functions. Despite the introduction of numerous anti-aging strategies, their therapeutic outcomes have often been less than optimal. Consequently, discovering new targets to mitigate aging effects is of critical importance. We applied Mendelian randomization (MR) to identify potential pharmacological targets against aging, drawing upon summary statistics from both the Decode and FinnGen cohorts, with further validation in an additional cohort. To address potential reverse causality, bidirectional MR analysis with Steiger filtering was utilized. Additionally, Bayesian co-localization and phenotype scanning were implemented to investigate previous associations between genetic variants and traits. Summary-data-based Mendelian randomization (SMR) analysis was conducted to assess the impact of genetic variants on aging via their effects on protein expression. Additionally, mediation analysis was orchestrated to uncover potential intermediaries in these associations. Finally, we probed the systemic implications of drug-target protein expression across diverse indications by MR-PheWas analysis. Utilizing a Bonferroni-corrected threshold, our MR examination identified 10 protein-aging associations. Within this cohort of proteins, MST1, LCT, GMPR2, PSMB4, ECM1, EFEMP1, and ISLR2 appear to exacerbate aging risks, while MAX, B3GNT8, and USP8 may exert protective influences. None of these proteins displayed reverse causality except EFEMP1. Bayesian co-localization inferred shared variants between aging and proteins such as B3GNT8 (rs11670143), ECM1 (rs61819393), and others listed. Mediator analysis pinpointed 1,5-anhydroglucitol as a partial intermediary in the influence LCT exhibits on telomere length. Circulating proteins play a pivotal role in influencing the aging process, making them promising candidates for therapeutic intervention. The implications of these proteins in aging warrant further investigation in future clinical research.

NMR metabolomic modeling of age and lifespan: A multicohort analysis

Chung-Ho E. Lau, Maria Manou, Georgios Markozannes, Mika Ala-Korpela, Yoav Ben-Shlomo, Nish Chaturvedi, Jorgen Engmann, Aleksandra Gentry-Maharaj, Karl-Heinz Herzig ... See all authors

Metabolomic age models have been proposed for the study of biological aging, however, they have not been widely validated. We aimed to assess the performance of newly developed and existing nuclear magnetic resonance spectroscopy (NMR) metabolomic age models for prediction of chronological age (CA), mortality, and age-related disease. Ninety-eight metabolic variables were measured in blood from nine UK and Finnish cohort studies (N ≈31,000 individuals, age range 24–86 years). We used nonlinear and penalized regression to model CA and time to all-cause mortality. We examined associations of four new and two previously published metabolomic age models, with aging risk factors and phenotypes. Within the UK Biobank (N ≈102,000), we tested prediction of CA, incident disease (cardiovascular disease (CVD), type-2 diabetes mellitus, cancer, dementia, and chronic obstructive pulmonary disease), and all-cause mortality. Seven-fold cross-validated Pearson's r between metabolomic age models and CA ranged between 0.47 and 0.65 in the training cohort set (mean absolute error: 8–9 years). Metabolomic age models, adjusted for CA, were associated with C-reactive protein, and inversely associated with glomerular filtration rate. Positively associated risk factors included obesity, diabetes, smoking, and physical inactivity. In UK Biobank, correlations of metabolomic age with CA were modest (r = 0.29–0.33), yet all metabolomic model scores predicted mortality (hazard ratios of 1.01 to 1.06/metabolomic age year) and CVD, after adjustment for CA. While metabolomic age models were only moderately associated with CA in an independent population, they provided additional prediction of morbidity and mortality over CA itself, suggesting their wider applicability.

Epigenetic age oscillates during the day

Karolis Koncevičius, Akhil Nair, Aušrinė Šveikauskaitė, Agnė Šeštokaitė, Auksė Kazlauskaitė, Audrius Dulskas, Artūras Petronis

Since their introduction, epigenetic clocks have been extensively used in aging, human disease, and rejuvenation studies. In this article, we report an intriguing pattern: epigenetic age predictions display a 24-h periodicity. We tested a circadian blood sample collection using 17 epigenetic clocks addressing different aspects of aging. Thirteen clocks exhibited significant oscillations with the youngest and oldest age estimates around midnight and noon, respectively. In addition, daily oscillations were consistent with the changes of epigenetic age across different times of day observed in an independant populational dataset. While these oscillations can in part be attributed to variations in white blood cell type composition, cell count correction methods might not fully resolve the issue. Furthermore, some epigenetic clocks exhibited 24-h periodicity even in the purified fraction of neutrophils pointing at plausible contributions of intracellular epigenomic oscillations. Evidence for circadian variation in epigenetic clocks emphasizes the importance of the time-of-day for obtaining accurate estimates of epigenetic age.

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PREPRINT

The Sociodemographic and Lifestyle Correlates of Epigenetic Aging in a Nationally Representative U.S. Study of Younger Adults

Kathleen Mullan Harris, Brandt Levitt, Lauren Gaydosh, Chantel Martin, Jess M. Meyer, Aura Ankita Mishra, Audrey L. Kelly, Allison E. Aiello

Participants Data come from the National Longitudinal Study of Adolescent to Adult Health, a national cohort of adolescents in grades 7-12 in U.S. in 1994 followed for 25 years over five interview waves. Our analytic sample includes participants followed-up through Wave V in 2016-18 who provided blood samples for DNA methylation (DNAm) testing (n=4237) at Wave V.

Exposure Sociodemographic (sex, race/ethnicity, immigrant status, socioeconomic status, geographic location) and lifestyle (obesity status, exercise, tobacco, and alcohol use) characteristics.

Main Outcome Biological aging assessed from blood DNAm using 16 epigenetic clocks when the cohort was aged 33-44 in Wave V.

Results While there is considerable variation in the mean and distribution of epigenetic clock estimates and in the correlations among the clocks, we found sociodemographic and lifestyle factors are more often associated with biological aging in clocks trained to predict current or dynamic phenotypes (e.g., PhenoAge, GrimAge and DunedinPACE) as opposed to clocks trained to predict chronological age alone (e.g., Horvath). Consistent and strong associations of faster biological aging were found for those with lower levels of education and income, and those with severe obesity, no weekly exercise, and tobacco use.

Conclusions and Relevance Our study found important social and lifestyle factors associated with biological aging in a nationally representative cohort of younger-aged adults. These findings indicate that molecular processes underlying disease risk can be identified in adults entering midlife before disease is manifest and represent useful targets for interventions to reduce social inequalities in heathy aging and longevity.

pyaging: a Python-based compendium of GPU-optimized aging clocks

Lucas Paulo de Lima Camillo [1]

Motivation: Aging is intricately linked to diseases and mortality. It is reflected in molecular changes across various tissues which can be leveraged for the development of biomarkers of aging using machine learning models, known as aging clocks. Despite advancements in the field, a significant challenge remains: the lack of robust, Python-based software tools for integrating and comparing these diverse models. This gap highlights the need for comprehensive solutions that can handle the complexity and variety of data in aging research.

Results: To address this gap, I introduce pyaging, a comprehensive open-source Python package designed to facilitate aging research. pyaging harmonizes dozens of aging clocks, covering a range of molecular data types such as DNA methylation, transcriptomics, histone mark ChIP-Seq, and ATAC-Seq. The package is not limited to traditional model types; it features a diverse array, from linear and principal component models to neural networks and automatic relevance determination models. Thanks to a PyTorch-based backend that enables GPU acceleration, pyaging is capable of rapid inference, even when dealing with large datasets and complex models. In addition, the package's support for multi-species analysis extends its utility across various organisms, including humans, various mammals, and Caenorhabditis elegans.

Genetic Correlates of Biological Aging and the Influence on Prediction of Mortality

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Oluwasefunmi Akeju, MBChB, MPH, Michelle M J Mens, PhD, Robert Warmerdam, BSc, Marjolein Dijkema, MSc, Anita H J van den Biggelaar, PhD, Lude Franke, PhD, Jaap Goudsmit, MD, PhD, Julia W Wu, ScD

Longevity and disease-free survival are influenced by a combination of genetics and lifestyle. Biological age (BioAge), a measure of aging based on composite biomarkers, may outperform chronological age in predicting health and longevity. This study investigated the relationship between genetic risks, lifestyle factors, and delta age (Δ_{age}), estimated as the difference between biological and chronological age. BioAge and Δ_{age} were calculated for 52 418 participants from the population-based Lifelines cohort. We computed 2 independent polygenic risk scores (PRS) for health span and DNA methylation-based aging clock to characterize genetic risks. The capacity of BioAge to predict all-cause mortality when adjusted for chronological age and genetic risks for aging, was assessed. Obesity, lifestyle, socioeconomic status, sex, and genetic variations in a population contributed to the differences in the rates of accelerated aging. The overall risk of death for a 1-year increase in BioAge for a given chronological age and sex among the genotyped participants was 11% (HR = 1.11; 95% CI: 1.09, 1.13). After adjusting for genetic factors, BioAge maintained its sensitivity for predicting mortality. Findings from this study ascertain that BioAge can be a useful tool for risk stratification in research and aging interventions.

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A p21–ATD mouse model for monitoring and eliminating senescent cells and its application in liver regeneration post injury

Cellular senescence associates with pathological aging and tissue dysfunctions. Studies utilizing mouse models for cell lineage tracings have emphasized the importance of senescence heterogeneity in different organs and cell types. Here, we constructed a p21- (Akaluc - tdTomato - Diphtheria Toxin Receptor [DTR]) (ATD) mouse model to specifically study the undefined mechanism for p21-expressing senescent cells in the aged and liver injury animals. The successful expressions of these genes enabled in vitro flow cytometric sorting, in vivo tracing, and elimination of p21-expressing senescent cells. During the natural aging process, p21-expressing cells were found in various tissues of p21-ATD mice. Eliminating p21-expressing cells in the aged p21-ATD mice recovered their multiple biological functions. p21-ATD/Fah$^{-/-}$ mice, bred from p21-ATD mice and fumarylacetoacetate hydrolase (Fah)$^{-/-}$ mice of liver injury, showed that the majority of their senescent hepatocytes were the phenotype of p21^{+} rather than p16^{+}. Furthermore, eliminating the p21-expressing hepatocytes significantly promoted the engraftment of grafted hepatocytes and facilitated liver repopulation, resulting in significant recovery from liver injury. Our p21-ATD mouse model serves as an optimal model for studying the pattern and function of p21-expressing senescent cells under the physical and pathological conditions during aging.

Human skeletal muscle aging atlas

Skeletal muscle aging is a key contributor to age-related frailty and sarcopenia with substantial implications for global health. Here we profiled 90,902 single cells and 92,259 single nuclei from 17 donors to map the aging process in the adult human intercostal muscle, identifying cellular changes in each muscle compartment. We found that distinct subsets of muscle stem cells exhibit decreased ribosome biogenesis genes and increased *CCL2* expression, causing different aging phenotypes. Our atlas also highlights an expansion of nuclei associated with the neuromuscular junction, which may reflect re-innervation, and outlines how the loss of fast-twitch myofibers is mitigated through regeneration and upregulation of fast-type markers in slow-twitch myofibers with age. Furthermore, we document the function of aging muscle microenvironment in immune cell attraction. Overall, we present a comprehensive human skeletal muscle aging resource (https://www.muscleageingcellatlas.org/) together with an in-house mouse muscle atlas to study common features of muscle aging across species.

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PREPRINT

Tissue and cellular spatiotemporal dynamics in colon aging

Aidan C. Daly, Francesco Cambuli, Tarmo Äijö, Britta Lötstedt, Nemanja Marjanovic, Olena Kuksenko, Matthew Smith-Erb, Sara Fernandez, Daniel Domovic, Nicholas Van Wittenberghe, Eugene Drokhlyansky, Gabriel K Griffin, Hemali Phatnani, Richard Bonneau, Aviv Regev, Sanja Vickovic

Tissue structure and molecular circuitry in the colon can be profoundly impacted by systemic age-related effects, but many of the underlying molecular cues remain unclear. Here, we built a cellular and spatial atlas of the colon across three anatomical regions and 11 age groups, encompassing ~1,500 mouse gut tissues profiled by spatial transcriptomics and ~400,000 single nucleus RNA-seq profiles. We developed a new computational framework, cSplotch, which learns a hierarchical Bayesian model of spatially resolved cellular expression associated with age, tissue region, and sex, by leveraging histological features to share information across tissue samples and data modalities. Using this model, we identified cellular and molecular gradients along the adult colonic tract and across the main crypt axis, and multicellular programs associated with aging in the large intestine. Our multi-modal framework for the investigation of cell and tissue organization can aid in the understanding of cellular roles in tissue-level pathology.

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Single-cell senescence identification reveals senescence heterogeneity, trajectory, and modulators

Wanyu Tao • Zhengqing Yu • Jing-Dong J. Han [3] • Show footnotes

Cellular senescence underlies many aging-related pathologies, but its heterogeneity poses challenges for studying and targeting senescent cells. We present here a machine learning program senescent cell identification (SenCID), which accurately identifies senescent cells in both bulk and single-cell transcriptome. Trained on 602 samples from 52 senescence transcriptome datasets spanning 30 cell types, SenCID identifies six major senescence identities (SIDs). Different SIDs exhibit different senescence baselines, stemness, gene functions, and responses to senolytics. SenCID enables the reconstruction of senescent trajectories under normal aging, chronic diseases, and COVID-19. Additionally, when applied to single-cell Perturb-seq data, SenCID helps reveal a hierarchy of senescence modulators. Overall, SenCID is an essential tool for precise single-cell analysis of cellular senescence, enabling targeted interventions against senescent cells.

C. elegans aging research

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PREPRINT

Mechanical stress through growth on stiffer substrates impacts animal health and longevity in *C. elegans*

Mechanical stress is a measure of internal resistance exhibited by a body or material when external forces, such as compression, tension, bending, etc. are applied. The study of mechanical stress on health and aging is a continuously growing field, as major changes to the extracellular matrix and cell-to-cell adhesions can result in dramatic changes to tissue stiffness during aging and diseased conditions. For example, during normal aging, many tissues including the ovaries, skin, blood vessels, and heart exhibit increased stiffness, which can result in a significant reduction in function of that organ. As such, numerous model systems have recently emerged to study the impact of mechanical and physical stress on cell and tissue health, including cell-culture conditions with matrigels and other surfaces that alter substrate stiffness and ex vivo tissue models that can apply stress directly to organs like muscle or tendons. Here, we sought to develop a novel method in an in vivo, model organism setting to study the impact of mechanical stress on aging, by increasing substrate stiffness in solid agar medium of *C. elegans*. To our surprise, we found shockingly limited impact of growth of *C. elegans* on stiffer substrates, including limited effects on cellular health, gene expression, organismal health, stress resilience, and longevity. Overall, our studies reveal that altering substrate stiffness of growth medium for *C. elegans* have only mild impact on animal health and longevity; however, these impacts were not nominal and open up important considerations for *C. elegans* biologists in standardizing agar medium choice for experimental assays.

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PREPRINT

Aging-associated decline of phosphatidylcholine synthesis is a malleable trigger of natural mitochondrial aging

Mitochondrial dysfunction is a prominent hallmark of aging contributing to the functional decline of metabolic plasticity in late life. While genetic distortions of mitochondrial integrity elicit premature aging, the mechanisms leading to "natural" aging of mitochondria are less clear. Here we initially used proteomics, genetics and functional tests in wild type *C. elegans* and long-lived *clk-1(qm30)* and *isp-1(qm150)* mitochondrial mutants to identify molecular pathways that safeguard longevity amid persistent mitochondrial inefficiency. Strikingly, these analyses and subsequent transcriptomic and functional tests in the human system revealed aging-associated decline of phosphatidylcholine (PC) synthesis as a trigger of mitochondrial network disruption, which contributes to mitochondrial dysfunction during normal aging. Moreover, we found that ectopic boosting of PC levels via diet restores late life mitochondrial integrity *in vivo* and rescues metabolic plasticity in cell culture tests. Our work thus uncovered a novel natural driver of mitochondrial aging that is malleable by dietary interventions.

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PREPRINT

ELO-6 expression predicts longevity in isogenic populations of *Caenorhabditis elegans*

Weilin Kong, Guoli Gu, Tong Dai, Beibei Chen, Mintie Pu

Variations of individual lifespans within genetically identical populations in homogenous environments are remarkable, with the cause largely unknown. Gene expression changes with age, and the transcriptome changes correlate with chronological aging. Here, we show that in *Caenorhabditis elegans*, the expression dynamic of the fatty acid elongase ELO-6 during aging predicts individual longevity in isogenic populations. The expression of *elo-6* is reduced with age. From adult day 5, ELO-6 expression level exhibits variation between individuals, and the expression level is positively correlated with adult lifespan and health span. Interventions that prolong longevity enhance the expression stability of ELO-6 during aging from adult day 4 to adult day 8, indicating ELO-6 is also a populational lifespan predictor. We performed transcriptome analysis in short-lived and long-lived isogenic worms and identified differentially expressed genes, which are enriched for PQM-1 binding sites. Decreasing *pqm-1* expression in young adults improved the homogeneity of ELO-6 levels between individuals and enhanced health span. Furthermore, we found reducing the expression of genes that are highly expressed in short-lived individuals, including PQM-1 target genes, enhanced ELO-6 expression stability with age and extended lifespan. Thus, our study identified ELO-6 as a predictor of individual and populational lifespan and revealed the role of *pqm-1* in restricting health span and possibly causing individual lifespan variation.

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Combinatorial transcriptomic and genetic dissection of insulin/IGF-1 signaling-regulated longevity in *Caenorhabditis elegans*

Classical genetic analysis is invaluable for understanding the genetic interactions underlying specific phenotypes, but requires laborious and subjective experiments to characterize polygenic and quantitative traits. Contrarily, transcriptomic analysis enables the simultaneous and objective identification of multiple genes whose expression changes are associated with specific phenotypes. Here, we conducted transcriptomic analysis of genes crucial for longevity using datasets with *daf-2*/insulin/IGF-1 receptor mutant *Caenorhabditis elegans*. Our analysis unraveled multiple epistatic relationships at the transcriptomic level, in addition to verifying genetically established interactions. Our combinatorial analysis also revealed transcriptomic changes associated with longevity conferred by *daf-2* mutations. In particular, we demonstrated that the extent of lifespan changes caused by various mutant alleles of the longevity transcription factor *daf-16*/*FOXO* matched their effects on transcriptomic changes in *daf-2* mutants. We identified specific aging-regulating signaling pathways and subsets of structural and functional RNA elements altered by different genes in *daf-2* mutants. Lastly, we elucidated the functional cooperation between several longevity regulators, based on the combination of transcriptomic and molecular genetic analysis. These data suggest that different biological processes coordinately exert their effects on longevity in biological networks. Together our work demonstrates the utility of transcriptomic dissection analysis for identifying important genetic interactions for physiological processes, including aging and longevity.

REVIEWS/COMMENTS/ METHODS/EDITORIALS

Perspective

Combining rejuvenation interventions in rodents: a milestone in biomedical gerontology whose time has come

Caitlin J. Lewis & Aubrey D. de Grey

Introduction

Longevity research has matured to the point where significantly postponing age-related decline in physical and mental function is now achievable in the laboratory and foreseeable in the clinic. The most promising strategies involve rejuvenation, i.e. reducing biological age, not merely slowing its progression.

Areas covered

We discuss therapeutic strategies for rejuvenation and results achieved thus far, with a focus on in vivo studies. We discuss the implications of interventions which act on mean or maximum lifespan and those showing effects in accelerated disease models. While the focus is on work conducted in mice, we also highlight notable insights in the field from studies in other model organisms.

Expert opinion

Rejuvenation was originally proposed as easier than slowing aging because it targets initially inert changes to tissue structure and composition, rather than trying to disentangle processes that both create aging damage and maintain life. While recent studies support this hypothesis, a true test requires a panel of rejuvenation interventions targeting multiple damage categories simultaneously. Considerations of cost, profitability, and academic significance have dampened enthusiasm for such work, but it is vital. Now is the time for the field to take this key step toward the medical control of aging.

Candidate molecular targets uncovered in mouse lifespan extension studies

Maria Vedunova, Olga Borysova, Grigory Kozlov, Anna-Maria Zharova, Ivan Morgunov & **Alexey Moskalev**

Introduction

Multiple interventions have demonstrated an increase in mouse lifespan. However, non-standardized controls, sex or strain-specific factors, and insufficient focus on targets, hinder the translation of these findings into clinical applications.

Areas covered

We examined the effects of genetic and drug-based interventions on mice from databases DrugAge, GenAge, the Mouse Phenome Database, and publications from PubMed that led to a lifespan extension of more than 10%, identifying specific molecular targets that were manipulated to achieve the maximum lifespan in mice. Subsequently, we characterized 10 molecular targets influenced by these interventions, with particular attention given to clinical trials and potential indications for each.

Expert opinion

To increase the translational potential of mice life-extension studies to clinical research several factors are crucial: standardization of mice lifespan research approaches, the development of clear criteria for control and experimental groups, the establishment of criteria for potential geroprotectors, and focusing on targets and their clinical application. Pinpointing the targets affected by geroprotectors helps in understanding species-specific differences and identifying potential side effects, ensuring the safety and effectiveness of clinical trials. Additionally, target review facilitates the optimization of treatment protocols and the evaluation of the clinical feasibility of translating research findings into practical therapies for humans.

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OPINION article

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This article is part of the Research Topic
Year in Review: Discussions in Genetics of Aging

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The quest to define senescence

Allen T. Esterly Heidi J. Zapata*

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Rejuvenating aged stem cells: therapeutic strategies to extend health and lifespan

Francesca Matteini [1 2], Sara Montserrat-Vazquez [1 2], M Carolina Florian [1 2 3 4]

Aging is associated with a global decline in stem cell function. To date, several strategies have been proposed to rejuvenate aged stem cells: most of these result in functional improvement of the tissue where the stem cells reside, but the impact on the lifespan of the whole organism has been less clearly established. Here, we review some of the most recent work dealing with interventions that improve the regenerative capacity of aged somatic stem cells in mammals and that might have important translational possibilities. Overall, we underscore that somatic stem cell rejuvenation represents a strategy to improve tissue homeostasis upon aging and present some recent approaches with the potential to affect health span and lifespan of the whole organism.

SuperAgers and centenarians, dynamics of healthy ageing with cognitive resilience

Md Ariful Islam [a], Ujala Sehar [a], Omme Fatema Sultana [a], Upasana Mukherjee [a], Malcolm Brownell [a], Sudhir Kshirsagar [a], P. Hemachandra Reddy [a b c d e f]

Graceful healthy ageing and extended longevity is the most desired goal for human race. The process of ageing is inevitable and has a profound impact on the gradual deterioration of our physiology and health since it triggers the onset of many chronic conditions like dementia, osteoporosis, diabetes, arthritis, cancer, and cardiovascular disease. However, some people who lived/live more than 100 years called 'Centenarians" and how do they achieve their extended lifespans are not completely understood. Studying these unknown factors of longevity is important not only to establish a longer human lifespan but also to manage and treat people with shortened lifespans suffering from age-related morbidities. Furthermore, older adults who maintain strong cognitive function are referred to as "SuperAgers" and may be resistant to risk factors linked to cognitive decline. Investigating the mechanisms underlying their cognitive resilience may contribute to the development of therapeutic strategies that support the preservation of cognitive function as people age. The key to a long, physically, and cognitively healthy life has been a mystery to scientists for ages. Developments in the medical sciences helps us to a better understanding of human physiological function and greater access to medical care has led us to an increase in life expectancy. Moreover, inheriting favorable genetic traits and adopting a healthy lifestyle play pivotal roles in promoting longer and healthier lives. Engaging in regular physical activity, maintaining a balanced diet, and avoiding harmful habits such as smoking contribute to overall well-being. The synergy between positive lifestyle choices, access to education, socio-economic factors, environmental determinants and genetic supremacy enhances the potential for a longer and healthier life. Our article aims to examine the factors associated with healthy ageing, particularly focusing on cognitive health in centenarians. We will also be discussing different aspects of ageing including genomic instability, metabolic burden, oxidative stress and inflammation, mitochondrial dysfunction, cellular senescence, immunosenescence, and sarcopenia.

Targeting aging and age-related diseases with vaccines

Aging is a major risk factor for numerous chronic diseases. Vaccination offers a promising strategy to combat these age-related diseases by targeting specific antigens and inducing immune responses. Here, we provide a comprehensive overview of recent advances in vaccine-based interventions targeting these diseases, including Alzheimer's disease, type II diabetes, hypertension, abdominal aortic aneurysm, atherosclerosis, osteoarthritis, fibrosis and cancer, summarizing current approaches for identifying disease-associated antigens and inducing immune responses against these targets. Further, we reflect on the recent development of vaccines targeting senescent cells, as a strategy for more broadly targeting underlying causes of aging and associated pathologies. In addition to highlighting recent progress in these areas, we discuss important next steps to advance the therapeutic potential of these vaccines, including improving and robustly demonstrating efficacy in human clinical trials, as well as rigorously evaluating the safety and long-term effects of these vaccine strategies.

Noncoding RNA Contribution to Aging and Lifespan

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Alejandro P Ugalde, PhD ✉, David Roiz-Valle, MSc, Lucas Moledo-Nodar, MSc, Xurde M Caravia, PhD, José M P Freije, PhD, Carlos López-Otín, PhD

Aging is a multifactorial process characterized by an age-related decline in organismal fitness. This deterioration is the major risk factor for chronic diseases such as cardiovascular pathologies, neurodegeneration, or cancer, and it represents one of the main challenges of modern society. Therefore, understanding why and how we age would be a fundamental pillar to design strategies to promote a healthy aging. In the last decades, the study of the molecular bases of disease has been revolutionized by the discovery of different types of noncoding RNAs (ncRNAs) with regulatory potential. In this work, we will review the implication of ncRNAs in aging, with the aim to provide a first approach to the different aging-associated ncRNAs, their mechanism of action, and their potential relevance as therapeutic targets and disease biomarkers.

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The senescence-associated secretory phenotype and its physiological and pathological implications

Boshi Wang, Jin Han, Jennifer H. Elisseeff & Marco Demaria

Cellular senescence is a state of terminal growth arrest associated with the upregulation of different cell cycle inhibitors, mainly p16 and p21, structural and metabolic alterations, chronic DNA damage responses, and a hypersecretory state known as the senescence-associated secretory phenotype (SASP). The SASP is the major mediator of the paracrine effects of senescent cells in their tissue microenvironment and of various local and systemic biological functions. In this Review, we discuss the composition, dynamics and heterogeneity of the SASP as well as the mechanisms underlying its induction and regulation. We describe the various biological properties of the SASP, its beneficial and detrimental effects in different physiological and pathological settings, and its impact on overall health span. Finally, we discuss the use of the SASP as a biomarker and of SASP inhibitors as senomorphic interventions to treat cancer and other age-related conditions.

Immunological aspects of central neurodegeneration

Mireia Niso-Santano, José M. Fuentes & Lorenzo Galluzzi

The etiology of various neurodegenerative disorders that mainly affect the central nervous system including (but not limited to) Alzheimer's disease, Parkinson's disease and Huntington's disease has classically been attributed to neuronal defects that culminate with the loss of specific neuronal populations. However, accumulating evidence suggests that numerous immune effector cells and the products thereof (including cytokines and other soluble mediators) have a major impact on the pathogenesis and/or severity of these and other neurodegenerative syndromes. These observations not only add to our understanding of neurodegenerative conditions but also imply that (at least in some cases) therapeutic strategies targeting immune cells or their products may mediate clinically relevant neuroprotective effects. Here, we critically discuss immunological mechanisms of central neurodegeneration and propose potential strategies to correct neurodegeneration-associated immunological dysfunction with therapeutic purposes.

Tricarboxylic Acid Cycle Intermediates and Individual Ageing

Natalia Kurhaluk [1]

Anti-ageing biology and medicine programmes are a focus of genetics, molecular biology, immunology, endocrinology, nutrition, and therapy. This paper discusses metabolic therapies aimed at prolonging longevity and/or health. Individual components of these effects are postulated to be related to the energy supply by tricarboxylic acid (TCA) cycle intermediates and free radical production processes. This article presents several theories of ageing and clinical descriptions of the top markers of ageing, which define ageing in different categories; additionally, their interactions with age-related changes and diseases related to α-ketoglutarate (AKG) and succinate SC formation and metabolism in pathological states are explained. This review describes convincingly the differences in the mitochondrial characteristics of energy metabolism in animals, with different levels (high and low) of physiological reactivity of functional systems related to the state of different regulatory systems providing oxygen-dependent processes. Much attention is given to the crucial role of AKG and SC in the energy metabolism in cells related to amino acid synthesis, epigenetic regulation, cell stemness, and differentiation, as well as metabolism associated with the development of pathological conditions and, in particular, cancer cells. Another goal was to address the issue of ageing in terms of individual characteristics related to physiological reactivity. This review also demonstrated the role of the Krebs cycle as a key component of cellular energy and ageing, which is closely associated with the development of various age-related pathologies, such as cancer, type 2 diabetes, and cardiovascular or neurodegenerative diseases where the mTOR pathway plays a key role. This article provides postulates of postischaemic phenomena in an ageing organism and demonstrates the dependence of accelerated ageing and age-related pathology on the levels of AKG and SC in studies on different species (roundworm *Caenorhabditis elegans*, *Drosophila*, mice, and humans used as models). The findings suggest that this approach may also be useful to show that Krebs cycle metabolites may be involved in age-related abnormalities of the mitochondrial metabolism and may thus induce epigenetic reprogramming that contributes to the senile phenotype and degenerative diseases. The metabolism of these compounds is particularly important when considering ageing mechanisms connected with different levels of initial physiological reactivity and able to initiate individual programmed ageing, depending on the intensity of oxygen consumption, metabolic peculiarities, and behavioural reactions.

Amino acid restriction, aging, and longevity: an update

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.

In the land of not-unhappiness: On the state-of-the-art of targeting aging and age-related diseases by biomedical research

Eirini Klinaki [1], Mikolaj Ogrodnik [2]

The concept of the Land of Not-Unhappiness refers to the potential achievement of eliminating the pathologies of the aging process. To inform of how close we are to settling in the land, we summarize and review the achievements of research on anti-aging interventions over the last hundred years with a specific focus on strategies that slow down metabolism, compensate for aging-related losses, and target a broad range of age-related diseases. We critically evaluate the existing interventions labeled as "anti-aging," such as calorie restriction, exercise, stem cell administration, and senolytics, to provide a down-to-earth evaluation of their current applicability in counteracting aging. Throughout the text, we have maintained a light tone to make it accessible to non-experts in biogerontology, and provide a broad overview for those considering conducting studies, research, or seeking to understand the scientific basis of anti-aging medicine.

Healthcare on the brink: navigating the challenges of an aging society in the United States

Charles H Jones [1], Mikael Dolsten [2]

The US healthcare system is at a crossroads. With an aging population requiring more care and a strained system facing workforce shortages, capacity issues, and fragmentation, innovative solutions and policy reforms are needed. This paper aims to spark dialogue and collaboration among healthcare stakeholders and inspire action to meet the needs of the aging population. Through a comprehensive analysis of the impact of an aging society, this work highlights the urgency of addressing this issue and the importance of restructuring the healthcare system to be more efficient, equitable, and responsive.

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It is time to explore the impact of length of gestation and fetal health on the human lifespan

Zhuo Yu, Yushan Dong, Yuhan Chen, Lotfi Aleya, Yinhuan Zhao, Lan Yao ✉, Weikuan Gu ✉

A recently proposed principal law of lifespan (PLOSP) proposes to extend the whole human lifespan by elongating different life stages. As the preborn stage of a human being, gestation is the foundation for the healthy development of the human body. The antagonistic pleiotropy (AP) theory of aging states that there is a trade-off between early life fitness and late-life mortality. The question is whether slower development during the gestation period would be associated with a longer lifespan. Among all living creatures, the length of the gestation period is highly positively correlated to the length of the lifespan, although such a correlation is thought to be influenced by the body sizes of different species. While examining the relationship between lifespan length and body size within the same species, dogs exhibit a negative correlation between lifespans and body sizes, while there is no such correlation among domestic cats. For humans, most adverse gestational environments shorten the period of gestation, and their impacts are long-term. While many issues remain unsolved, various developmental features have been linked to the conditions during the gestation period. Given that the length of human pregnancies can vary randomly by as long as 5 weeks, it is worth investigating whether a slow steady healthy gestation over a longer period will be related to a longer and healthier lifespan. This article discusses the potential benefits, negative impacts, and challenges of the relative elongation of the gestation period.

OTHER RESEARCH & REVIEWS

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A pan-cancer analysis of the microbiome in metastatic cancer

Thomas W. Battaglia [13] • Iris L. Mimpen [13] • Joleen J.H. Traets • ... Lodewyk Wessels [14] •
Joris van de Haar [14] • Emile Voest [14, 15] • Show all authors • Show footnotes

Microbial communities are resident to multiple niches of the human body and are important modulators of the host immune system and responses to anticancer therapies. Recent studies have shown that complex microbial communities are present within primary tumors. To investigate the presence and relevance of the microbiome in metastases, we integrated mapping and assembly-based metagenomics, genomics, transcriptomics, and clinical data of 4,160 metastatic tumor biopsies. We identified organ-specific tropisms of microbes, enrichments of anaerobic bacteria in hypoxic tumors, associations between microbial diversity and tumor-infiltrating neutrophils, and the association of Fusobacterium with resistance to immune checkpoint blockade (ICB) in lung cancer. Furthermore, longitudinal tumor sampling revealed temporal evolution of the microbial communities and identified bacteria depleted upon ICB. Together, we generated a pan-cancer resource of the metastatic tumor microbiome that may contribute to advancing treatment strategies.

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Telomere dysfunction alters intestinal stem cell dynamics to promote cancer

Kyle A. LaBella • Wen-Hao Hsu • Jiexi Li • ... Jianhua Zhang • Yan Xia • Ronald A. DePinho [4] •

Telomere dynamics are linked to aging hallmarks, and age-associated telomere loss fuels the development of epithelial cancers. In *Apc*-mutant mice, the onset of DNA damage associated with telomere dysfunction has been shown to accelerate adenoma initiation via unknown mechanisms. Here, we observed that *Apc*-mutant mice engineered to experience telomere dysfunction show accelerated adenoma formation resulting from augmented cell competition and clonal expansion. Mechanistically, telomere dysfunction induces the repression of EZH2, resulting in the derepression of Wnt antagonists, which causes the differentiation of adjacent stem cells and a relative growth advantage to *Apc*-deficient telomere dysfunctional cells. Correspondingly, in this mouse model, GSK3β inhibition countered the actions of Wnt antagonists on intestinal stem cells, resulting in impaired adenoma formation of telomere dysfunctional *Apc*-mutant cells. Thus, telomere dysfunction contributes to cancer initiation through altered stem cell dynamics, identifying an interception strategy for human *APC*-mutant cancers with shortened telomeres.

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PREPRINT

Single-cell genomics and regulatory networks for 388 human brains

Single-cell genomics is a powerful tool for studying heterogeneous tissues such as the brain. Yet, little is understood about how genetic variants influence cell-level gene expression. Addressing this, we uniformly processed single-nuclei, multi-omics datasets into a resource comprising >2.8M nuclei from the prefrontal cortex across 388 individuals. For 28 cell types, we assessed population-level variation in expression and chromatin across gene families and drug targets. We identified >550K cell-type-specific regulatory elements and >1.4M single-cell expression-quantitative-trait loci, which we used to build cell-type regulatory and cell-to-cell communication networks. These networks manifest cellular changes in aging and neuropsychiatric disorders. We further constructed an integrative model accurately imputing single-cell expression and simulating perturbations; the model prioritized ~250 disease-risk genes and drug targets with associated cell types.

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Spatial proteomics in neurons at single-protein resolution

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To understand biological processes, it is necessary to reveal the molecular heterogeneity of cells by gaining access to the location and interaction of all biomolecules. Significant advances were achieved by super-resolution microscopy, but such methods are still far from reaching the multiplexing capacity of proteomics. Here, we introduce secondary label-based unlimited multiplexed DNA-PAINT (SUM-PAINT), a high-throughput imaging method that is capable of achieving virtually unlimited multiplexing at better than 15 nm resolution. Using SUM-PAINT, we generated 30-plex single-molecule resolved datasets in neurons and adapted omics-inspired analysis for data exploration. This allowed us to reveal the complexity of synaptic heterogeneity, leading to the discovery of a distinct synapse type. We not only provide a resource for researchers, but also an integrated acquisition and analysis workflow for comprehensive spatial proteomics at single-protein resolution.

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PREPRINT

Rapid evolution of genes with anti-cancer functions during the origins of large bodies and cancer resistance in elephants

Jacob Bowman, Vincent J. Lynch

Elephants have emerged as a model system to study the evolution of body size and cancer resistance because, despite their immense size, they have a very low prevalence of cancer. Previous studies have found that duplication of tumor suppressors at least partly contributes to the evolution of anti-cancer cellular phenotypes in elephants. Still, many other mechanisms must have contributed to their augmented cancer resistance. Here, we use a suite of codon-based maximum-likelihood methods and a dataset of 13,310 protein-coding gene alignments from 261 *Eutherian* mammals to identify positively selected and rapidly evolving elephant genes. We found 496 genes (3.73% of alignments tested) with statistically significant evidence for positive selection and 660 genes (4.96% of alignments tested) that likely evolved rapidly in elephants. Positively selected and rapidly evolving genes are statistically enriched in gene ontology terms and biological pathways related to regulated cell death mechanisms, DNA damage repair, cell cycle regulation, epidermal growth factor receptor (EGFR) signaling, and immune functions, particularly neutrophil granules and degranulation. All of these biological factors are plausibly related to the evolution of cancer resistance. Thus, these positively selected and rapidly evolving genes are promising candidates for genes contributing to elephant-specific traits, including the evolution of molecular and cellular characteristics that enhance cancer resistance.