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Sven Bulterijs

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The effect of the COVID-19 pandemic on life expectancy in 27 countries

Guogui Huang ✉, Fei Guo, Klaus F. Zimmermann, Lihua Liu, Lucy Taksa, Zhiming Cheng, Massimiliano Tani & Marika Franklin

The expected year-on-year intrinsic mortality variations/changes are largely overlooked in the existing research when estimating the effect of the COVID-19 pandemic on mortality patterns. To fill this gap, this study provides a new assessment of the loss of life expectancy caused by COVID-19 in 27 countries considering both the actual and the expected changes in life expectancy between 2019 and 2020. Life expectancy in 2020 and the expected life expectancy in the absence of COVID-19 are estimated using the Lee-Carter model and data primarily from the Human Mortality Database. The results show that life expectancy in 21 of the 27 countries was expected to increase in 2020 had COVID-19 not occurred. By considering the expected mortality changes between 2019 and 2020, the study shows that, on average, the loss of life expectancy among the 27 countries in 2020 amounted to 1.33 year (95% CI 1.29–1.37) at age 15 and 0.91 years (95% CI 0.88–0.94) at age 65. Our results suggest that if the year-on-year intrinsic variations/changes in mortality were considered, the effects of COVID-19 on mortality are more profound than previously understood. This is particularly prominent for countries experiencing greater life expectancy increase in recent years.

Viral emissions into the air and environment after SARS-CoV-2 human challenge: a phase 1, open label, first-in-human study

Findings

Between March 6 and July 8, 2021, 36 participants (ten female and 26 male) were recruited and 18 (53%) of 34 participants became infected, resulting in protracted high viral loads in the nose and throat following a short incubation period, with mild-to-moderate symptoms. Two participants were excluded from the per-protocol analysis owing to seroconversion between screening and inoculation, identified post hoc. Viral RNA was detected in 63 (25%) of 252 Coriolis air samples from 16 participants, 109 (43%) of 252 mask samples from 17 participants, 67 (27%) of 252 hand swabs from 16 participants, and 371 (29%) of 1260 surface swabs from 18 participants. Viable SARS-CoV-2 was collected from breath captured in 16 masks and from 13 surfaces, including four small frequently touched surfaces and nine larger surfaces where airborne virus could deposit. Viral emissions correlated more strongly with viral load in nasal swabs than throat swabs. Two individuals emitted 86% of airborne virus, and the majority of airborne virus collected was released on 3 days. Individuals who reported the highest total symptom scores were not those who emitted most virus. Very few emissions occurred before the first reported symptom (7%) and hardly any before the first positive lateral flow antigen test (2%).

COGNITIVE REJUVENATION IN OLD RATS BY HIPPOCAMPAL OSKM GENE THERAPY

Steve Horvath, Ezequiel Lacunza, Martina Canatelli Mallat, Enrique L. Portiansky, Maria D. Gallardo, Robert T. Brooke, Priscila Chiavellini, Diana C. Pasquini, Mauricio Girard, Marianne Lehmann, Qi Yan, Ake T. Lu, Amin Haghani, Juozas Gordevicius, Martin Abba, Rodolfo G. Goya

Impaired performance in spatial learning and memory during aging in rats is associated with morphological and molecular changes in the brain, particularly in the hippocampus. Here, we assessed the cognitive performance of young (3.5 mo.) untreated rats and old (25.3 mo.) treated and control rats. Treatment was carried out by intrahippocampal injection of an adenovector that carries the GFP reporter gene as well as the 4 Yamanaka genes.

Learning and spatial memory performance were assessed by means of the Barnes maze test. The learning performance of the OSKM-treated old rats was significantly improved compared to that of the control old counterparts. A marginal (P=0.06) improvement in the spatial memory was recorded in the treated versus control old rats. OSKM gene expression induced no pathological changes in the brain. The morphology and number of hippocampal cell populations like astrocytes and mature neurons did not show any changes with the treatment in the old rats as compared with the control old counterparts. The rat pan tissue DNAm age marker revealed that old OSKM gene-treated rats show a trend towards a decrease in epigenetic age. The Limma package was used to assess differential methylation by fitting linear models to the methylation data for specific group comparisons. Comparison of differential methylation between old treated and old control hippocampal DNA samples identified 671 differentially methylated CpGs probes (DPMs) in the DNA of OSKM-treated hippocampi (p<0.05). Assessment of the DPMs in old versus young controls revealed the presence of 1,279 hypomethylated CpGs near the promoter regions in young hippocampi (versus old controls) and 914 hypermethylated CpGs near the promoter in young hippocampi compared to old control hippocampi. We found a subset of 174 hypomethylated CpGs in the hippocampal DNA from old OSKM rats and young controls both compared with old control hippocampi. This means that in the hippocampal DNA there is a common set of CpGs which are hypermethylated during aging and are demethylated by the OSKM genes. This observation suggested that in these 174 CpGs the hypermethylation induced by aging is reversed by the demethylation effect of the OSKM genes on the same 174 CpGs. This observation can be interpreted as a rejuvenation effect of the OSKM genes of the old hippocampal methylome. Our results extend to the rat the evidence that viral vector-mediated delivery of the Yamanaka genes in the brain has strong regenerative effects without adverse side effects.

Taurine deficiency as a driver of aging

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Editor's summary

Aging is associated with physiological changes that range in scale from organelles to organ systems, but we are still working to understand the molecular basis for these changes. Studying various animals, Singh *et al*. found that the amount of the semi-essential amino acid taurine in circulation decreased with age (see the Perspective by McGaunn and Baur). Supplementation with taurine slowed key markers of aging such as increased DNA damage, telomerase deficiency, impaired mitochondrial function, and cellular senescence. Loss of taurine in humans was associated with aging-related diseases, and concentrations of taurine and its metabolites increased in response to exercise. Taurine supplementation improved life span in mice and health span in monkeys. —L. Bryan Ray

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Distinct longevity mechanisms across and within species and their association with aging

Alexander Tyshkovskiy [10] • Siming Ma [10] • Anastasia V. Shindyapina [10] • ... Sergey E. Dmitriev •
Richard A. Miller • Vadim N. Gladyshev [11] ✉ • Show all authors • Show footnotes

Lifespan varies within and across species, but the general principles of its control remain unclear. Here, we conducted multi-tissue RNA-seq analyses across 41 mammalian species, identifying longevity signatures and examining their relationship with transcriptomic biomarkers of aging and established lifespan-extending interventions. An integrative analysis uncovered shared longevity mechanisms within and across species, including downregulated *Igf1* and upregulated mitochondrial translation genes, and unique features, such as distinct regulation of the innate immune response and cellular respiration. Signatures of long-lived species were positively correlated with age-related changes and enriched for evolutionarily ancient essential genes, involved in proteolysis and PI3K-Akt signaling. Conversely, lifespan-extending interventions counteracted aging patterns and affected younger, mutable genes enriched for energy metabolism. The identified biomarkers revealed longevity interventions, including KU0063794, which extended mouse lifespan and healthspan. Overall, this study uncovers universal and distinct strategies of lifespan regulation within and across species and provides tools for discovering longevity interventions.

Transcriptional profiling of aging tissues from female and male African turquoise killifish

Alan Xu, Bryan B. Teefy, Ryan J. Lu, Séverine Nozownik, Alexandra M. Tyers, Dario R. Valenzano, Bérénice A. Benayoun

The African turquoise killifish is an emerging vertebrate model organism with great potential for aging research due to its naturally short lifespan. Thus far, turquoise killifish aging 'omic' studies using RNA-seq have examined a single organ, single sex and/or evaluated samples from non-reference strains. Here, we describe a resource dataset of ribosomal RNA depleted RNA-seq libraries generated from the brain, heart, muscle, and spleen from both sexes, as well as young and old animals, in the reference GRZ turquoise killifish strain. We provide basic quality control steps and demonstrate the utility of our dataset by performing differential gene expression and gene ontology analyses by age and sex. Importantly, we show that age has a greater impact than sex on transcriptional landscapes across probed tissues. Finally, we confirm transcription of transposable elements (TEs), which are highly abundant and increase in expression with age in brain tissue. This dataset will be a useful resource for exploring gene and TE expression as a function of both age and sex in a powerful naturally short-lived vertebrate model.

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Cross-sectional analysis of healthy individuals across decades: Aging signatures across multiple physiological compartments

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Affiliations + expand

Abstract

The study of age-related biomarkers from different biofluids and tissues within the same individual might provide a more comprehensive understanding of age-related changes within and between compartments as these changes are likely highly interconnected. Understanding age-related differences by compartments may shed light on the mechanism of their reciprocal interactions, which may contribute to the phenotypic manifestations of aging. To study such possible interactions, we carried out a targeted metabolomic analysis of plasma, skeletal muscle, and urine collected from healthy participants, age 22-92 years, and identified 92, 34, and 35 age-associated metabolites, respectively. The metabolic pathways that were identified across compartments included inflammation and cellular senescence, microbial metabolism, mitochondrial health, sphingolipid metabolism, lysosomal membrane permeabilization, vascular aging, and kidney function.

Hypoxia extends lifespan and neurological function in a mouse model of aging

Robert S. Rogers, Hong Wang, Timothy J. Durham, Jonathan A. Stefely, Norah A. Owiti, Andrew L. Markhard, Lev Sandler, Tsz-Leung To, Vamsi K. Mootha ✉

There is widespread interest in identifying interventions that extend healthy lifespan. Chronic continuous hypoxia delays the onset of replicative senescence in cultured cells and extends lifespan in yeast, nematodes, and fruit flies. Here, we asked whether chronic continuous hypoxia is beneficial in mammalian aging. We utilized the *Ercc1 Δ/-* mouse model of accelerated aging given that these mice are born developmentally normal but exhibit anatomic, physiological, and biochemical features of aging across multiple organs. Importantly, they exhibit a shortened lifespan that is extended by dietary restriction, the most potent aging intervention across many organisms. We report that chronic continuous 11% oxygen commenced at 4 weeks of age extends lifespan by 50% and delays the onset of neurological debility in *Ercc1 Δ/-* mice. Chronic continuous hypoxia did not impact food intake and did not significantly affect markers of DNA damage or senescence, suggesting that hypoxia did not simply alleviate the proximal effects of the *Ercc1* mutation, but rather acted downstream via unknown mechanisms. To the best of our knowledge, this is the first study to demonstrate that "oxygen restriction" can extend lifespan in a mammalian model of aging.

Alcohol consumption and all-cause and cause-specific mortality among US adults: prospective cohort study

Yalan Tian, Jiahui Liu, Yue Zhao, Nana Jiang, Xiao Liu, Gang Zhao & Xia Wang ✉

Results

During an average follow-up of 12.65 years, among the 918,529 participants (mean age 46.1 years; 48.0% male), 141,512 adults died from all causes, 43,979 from cardiovascular disease (CVD), 33,222 from cancer, 8246 from chronic lower respiratory tract diseases, 5572 from accidents (unintentional injuries), 4776 from Alzheimer's disease, 4845 from diabetes mellitus, 2815 from influenza and pneumonia, and 2692 from nephritis, nephrotic syndrome, or nephrosis. Compared with lifetime abstainers, current infrequent, light, or moderate drinkers were at a lower risk of mortality from all causes [infrequent—hazard ratio: 0.87; 95% confidence interval: 0.84 to 0.90; light: 0.77; 0.75 to 0.79; moderate 0.82; 0.80 to 0.85], CVD, chronic lower respiratory tract diseases, Alzheimer's disease, and influenza and pneumonia. Also, light or moderate drinkers were associated with lower risk of mortality from diabetes mellitus and nephritis, nephrotic syndrome, or nephrosis. In contrast, heavy drinkers had a significantly higher risk of mortality from all causes, cancer, and accidents (unintentional injuries). Furthermore, binge drinking ≥ 1 day/week was associated with a higher risk of mortality from all causes (1.15; 1.09 to 1.22), cancer (1.22; 1.10 to 1.35), and accidents (unintentional injuries) (1.39; 1.11 to 1.74).

The Role of Respiratory Complex IV in Lifespan Length and Quality

Mitochondria play a pivotal role in lifespan regulation, though the underlying mechanisms remain elusive. As ageing progresses, damaged mitochondria with reduced ATP production and increased Reactive Oxygen Species (ROS) generation accumulate, yet mitochondrial depletion extends the lifespan of various animal models. Our previous research demonstrated that complex I (CI) activity during development but not adulthood is crucial for determining the lifespan of *Drosophila melanogaster*. Still, CI-deficient mitochondria do not generate excessive ROS, failing to recapitulate mitochondrial ageing. In this study, we focus on complex IV (CIV), whose depletion leads to the accumulation of "old-mitochondria", i.e. producing less ATP and more ROS. We reveal that CIV's role in longevity is more intricate than CI's, shaping lifespan through two "windows of opportunity". The first window, shared by CI and CIV, occurs during development. Small perturbations in CIV during development lead to the emergence of short-lived flies. These flies exhibit an adult phenotype reminiscent of mitochondrial- associated diseases, primarily characterised by their inability to store fat efficiently. Accordingly, partial complementation of CIV function using an alternative oxidase (AOX) restores molecular and physiological phenotypes. The second window emerges during fly senescence, where CIV deficiency curtails lifespan without hastening ageing—flies die earlier but not more rapidly. Notably, only the developmental phenotype is associated with TOR dysregulation and altered autophagy, emphasising that developmental dysfunction uniquely interferes with nutrient sensing and the main cellular recycling pathway. This study sheds light on the multifaceted role of mitochondrial complex IV in modulating lifespan, providing potential targets for interventions to foster healthy ageing.

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B cell-specific knockout of AID protects against atherosclerosis

Talin Ebrahimian ✉, France Dierick, Vincent Ta, Maria Kotsiopriftis, Jonathan O'Connor Miranda, Koren K. Mann, Alexandre Orthwein & Stephanie Lehoux ✉

Antigen-naive IgM-producing B cells are atheroprotective, whereas mature B cells producing class-switched antibodies promote atherosclerosis. Activation-induced cytidine deaminase (AID), which mediates class switch recombination (CSR), would thus be expected to foster atherosclerosis. Yet, AID also plays a major role in the establishment of B cell tolerance. We sought to define whether AID affects atherosclerotic plaque formation. We generated $Ldlr^{-/-}$ chimeras transplanted with bone marrow from $Aicda^{-/-}$ or wild-type (WT) mice, fed a HFD for 14 weeks. Decreased B cell maturation in $Ldlr^{-/-}Aicda^{-/-}$ mice was demonstrated by 50% reduction in splenic and aortic BAFFR expression, a key signaling component of B2 cell maturation. This was associated with increased plasma IgM in $Ldlr^{-/-}Aicda^{-/-}$ compared with $Ldlr^{-/-}$WT animals. Importantly, $Ldlr^{-/-}Aicda^{-/-}$ mice had reduced atherosclerotic lesion area ($0.20 \pm 0.03mm^2$) compared with $Ldlr^{-/-}$WT ($0.30 \pm 0.04mm^2$, $P < 0.05$), although no differences in plaque composition were noted between groups. In addition, immunofluorescence analysis revealed increased splenic B and T cell areas independent of cell number. AID depletion directly inhibits atherosclerotic plaque formation.

Gene expressions associated with longer lifespan and aging exhibit similarity in mammals ⊙

Masaki Takasugi ✉, Yuya Yoshida, Yoshiki Nonaka, Naoko Ohtani ✉   Author Notes

Abstract

Although molecular features underlying aging and species maximum lifespan (MLS) have been comprehensively studied by transcriptome analyses, the actual impact of transcriptome on aging and MLS remains elusive. Here, we found that transcriptional signatures that are associated with mammalian MLS exhibited significant similarity to those of aging. Moreover, transcriptional signatures of longer MLS and aging both exhibited significant similarity to that of longer-lived mouse strains, suggesting that gene expression patterns associated with species MLS contribute to extended lifespan even within a species and that aging-related gene expression changes overall represent adaptations that extend lifespan rather than deterioration. Finally, we found evidence of co-evolution of MLS and promoter sequences of MLS-associated genes, highlighting the evolutionary contribution of specific transcription factor binding motifs such as that of E2F1 in shaping MLS-associated gene expression signature. Our results highlight the importance of focusing on adaptive aspects of aging transcriptome and demonstrate that cross-species genomics can be a powerful approach for understanding adaptive aging transcriptome.

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Whole-genome methylation analysis of aging human tissues identifies age-related changes in developmental and neurological pathways

Ravi Tharakan, Ceereena Ubaida-Mohien, Christopher Dunn, Mary Kaileh, Rakel Tryggvadottir, Linda Zukley, Chee W. Chia, Ranjan Sen, Luigi Ferrucci ✉

Age-associated changes in the DNA methylation state can be used to assess the pace of aging. However, it is not understood what mechanisms drive these changes and whether these changes affect the development of aging phenotypes and the aging process in general. This study was aimed at gaining a more comprehensive understanding of aging-related methylation changes across the whole genome, and relating these changes to biological functions. It has been shown that skeletal muscle and blood monocytes undergo typical changes with aging. Using whole-genome bisulfite sequencing, we sought to characterize the genome-wide changes in methylation of DNA derived from both skeletal muscle and blood monocytes, and link these changes to specific genes and pathways through enrichment analysis. We found that methylation changes occur with aging at the locations enriched for developmental and neuronal pathways regulated in these two peripheral tissues. These results contribute to our understanding of changes in epigenome in human aging.

Long ant life span is maintained by a unique heat shock factor

Karl M. Glastad[1,2], Julian Roessler[3], Janko Gospocic[1,2], Roberto Bonasio[1,2] and Shelley L. Berger[1,2,3,4]

Eusocial insect reproductive females show strikingly longer life spans than nonreproductive female workers despite high genetic similarity. In the ant *Harpegnathos saltator* (*Hsal*), workers can transition to reproductive "gamergates," acquiring a fivefold prolonged life span by mechanisms that are poorly understood. We found that gamergates have elevated expression of heat shock response (HSR) genes in the absence of heat stress and enhanced survival with heat stress. This HSR gene elevation is driven in part by gamergate-specific up-regulation of the gene encoding a truncated form of a heat shock factor most similar to mammalian HSF2 (hsalHSF2). In workers, hsalHSF2 was bound to DNA only upon heat stress. In gamergates, hsalHSF2 bound to DNA even in the absence of heat stress and was localized to gamergate-biased HSR genes. Expression of hsalHSF2 in *Drosophila melanogaster* led to enhanced heat shock survival and extended life span in the absence of heat stress. Molecular characterization illuminated multiple parallels between long-lived flies and gamergates, underscoring the centrality of hsalHSF2 to extended ant life span. Hence, ant caste-specific heat stress resilience and extended longevity can be transferred to flies via hsalHSF2. These findings reinforce the critical role of proteostasis in health and aging and reveal novel mechanisms underlying facultative life span extension in ants.

Comparative analysis of bats and rodents' genomes suggests a relation between non-LTR retrotransposons, cancer incidence, and ageing

Marco Ricci, Valentina Peona ✉, Alessio Boattini & Cristian Taccioli

The presence in nature of species showing drastic differences in lifespan and cancer incidence has recently increased the interest of the scientific community. In particular, the adaptations and the genomic features underlying the evolution of cancer-resistant and long-lived organisms have recently focused on transposable elements (TEs). In this study, we compared the content and dynamics of TE activity in the genomes of four rodent and six bat species exhibiting different lifespans and cancer susceptibility. Mouse, rat, and guinea pig genomes (short-lived and cancer-prone organisms) were compared with that of naked mole rat (*Heterocephalus glaber*) which is a cancer-resistant organism and the rodent with the longest lifespan. The long-lived bats of the genera *Myotis*, *Rhinolophus*, *Pteropus* and *Rousettus* were instead compared with *Molossus molossus*, which is one of the organisms with the shortest lifespan among the order Chiroptera. Despite previous hypotheses stating a substantial tolerance of TEs in bats, we found that long-lived bats and the naked mole rat share a marked decrease of non-LTR retrotransposons (LINEs and SINEs) accumulation in recent evolutionary times.

Cellular Allostatic Load is linked to Increased Energy Expenditure and Accelerated Biological Aging

Stress triggers anticipatory physiological responses that promote survival, a phenomenon termed allostasis. However, the chronic activation of energy-dependent allostatic responses results in allostatic load, a dysregulated state that predicts functional decline, accelerates aging, and increases mortality in humans. The energetic cost and cellular basis for the damaging effects of allostatic load have not been defined. Here, by longitudinally profiling three unrelated primary human fibroblast lines across their lifespan, we find that chronic glucocorticoid exposure increases cellular energy expenditure by ~60%, along with a metabolic shift from glycolysis to mitochondrial oxidative phosphorylation (OxPhos). This state of stress-induced hypermetabolism is linked to mtDNA instability, non-linearly affects age-related cytokines secretion, and accelerates cellular aging based on DNA methylation clocks, telomere shortening rate, and reduced lifespan. Pharmacologically normalizing OxPhos activity while further increasing energy expenditure exacerbates the accelerated aging phenotype, pointing to total energy expenditure as a potential driver of aging dynamics. Together, our findings define bioenergetic and multi-omic recalibrations of stress adaptation, underscoring increased energy expenditure and accelerated cellular aging as interrelated features of cellular allostatic load.

Increased alcohol dehydrogenase 1 activity promotes longevity

Abbas Ghaddar [5] • Vinod K. Mony [5] • Swarup Mishra • ... Mary Kate Horak • Jeffrey S. Smith •
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Several molecules can extend healthspan and lifespan across organisms. However, most are upstream signaling hubs or transcription factors orchestrating complex anti-aging programs. Therefore, these molecules point to but do not reveal the fundamental mechanisms driving longevity. Instead, downstream effectors that are necessary and sufficient to promote longevity across conditions or organisms may reveal the fundamental anti-aging drivers. Toward this goal, we searched for effectors acting downstream of the transcription factor EB (TFEB), known as HLH-30 in *C. elegans*, because TFEB/HLH-30 is necessary across anti-aging interventions and its overexpression is sufficient to extend *C. elegans* lifespan and reduce biomarkers of aging in mammals including humans. As a result, we present an alcohol-dehydrogenase-mediated anti-aging response (AMAR) that is essential for *C. elegans* longevity driven by HLH-30 overexpression, caloric restriction, mTOR inhibition, and insulin-signaling deficiency. The sole overexpression of ADH-1 is sufficient to activate AMAR, which extends healthspan and lifespan by reducing the levels of glycerol—an age-associated and aging-promoting alcohol. *Adh1* overexpression is also sufficient to promote longevity in yeast, and *adh-1* orthologs are induced in calorically restricted mice and humans, hinting at ADH-1 acting as an anti-aging effector across phyla.

Whole-genome methylation analysis of aging human tissues identifies age-related changes in developmental and neurological pathways

Ravi Tharakan, Ceereena Ubaida-Mohien, Christopher Dunn, Mary Kaileh, Rakel Tryggvadottir, Linda Zukley, Chee W. Chia, Ranjan Sen, Luigi Ferrucci ✉

Age-associated changes in the DNA methylation state can be used to assess the pace of aging. However, it is not understood what mechanisms drive these changes and whether these changes affect the development of aging phenotypes and the aging process in general. This study was aimed at gaining a more comprehensive understanding of aging-related methylation changes across the whole genome, and relating these changes to biological functions. It has been shown that skeletal muscle and blood monocytes undergo typical changes with aging. Using whole-genome bisulfite sequencing, we sought to characterize the genome-wide changes in methylation of DNA derived from both skeletal muscle and blood monocytes, and link these changes to specific genes and pathways through enrichment analysis. We found that methylation changes occur with aging at the locations enriched for developmental and neuronal pathways regulated in these two peripheral tissues. These results contribute to our understanding of changes in epigenome in human aging.

C. elegans aging research

Calcineurin inhibition enhances *Caenorhabditis elegans* lifespan by defecation defects-mediated calorie restriction and nuclear hormone signaling

Priyanka Das, ⓘD Alejandro Aballay, ⓘD Jogender Singh

Calcineurin is a highly conserved calcium/calmodulin-dependent serine/threonine protein phosphatase with diverse functions. Inhibition of calcineurin is known to enhance *Caenorhabditis elegans* lifespan via multiple signaling pathways. Aiming to study the role of calcineurin in regulating innate immunity, we discover that calcineurin is required for the rhythmic defecation motor program (DMP) in *C. elegans*. Calcineurin inhibition leads to defects in the DMP, resulting in intestinal bloating, rapid colonization of the gut by bacteria, and increased susceptibility to bacterial infection. We demonstrate that intestinal bloating by calcineurin inhibition mimics calorie restriction that results in enhanced lifespan. The TFEB ortholog, HLH-30, is required for calcineurin inhibition-mediated lifespan enhancement by triggering lipolysis. Finally, we show that the nuclear hormone receptor, NHR-8, is upregulated by calcineurin inhibition and is required for increased lifespan. Our studies uncover a role for calcineurin in the *C. elegans* DMP and provide a new mechanism for calcineurin inhibition-mediated longevity extension.

Exosome-mediated delivery of superoxide dismutase for anti-aging studies in Caenorhabditis elegans

Xinxin Shao [1], Mengzhu Zhang [1], Yingxuan Chen [1], Siyu Sun [1], Shengcai Yang [2], Quanshun Li [3]

Affiliations + expand

Abstract

Aging is a dynamic and progressive process mediated by reactive oxygen species (ROS), and the antioxidant enzyme superoxide dismutase (SOD) can effectively scavenge ROS to extend longevity. However, the instability and impermeability of native enzyme limit its in vivo biomedical application. Currently, exosome as protein carriers attracts considerable attention in the disease treatment owing to low immunogenicity and high stability. Herein, SOD was encapsulated into exosomes via mechanical extrusion with saponin permeabilization to obtain SOD-loaded EXO (SOD@EXO). SOD@EXO with a hydrodynamic diameter of 101.7 ± 5.6 nm could scavenge excessive ROS and protect the cells from oxidative damage induced by 1-methyl-4-phenylpyridine. Compared with native SOD, SOD@EXO significantly extended the lifespan of N2 wild-type Caenorhabditis elegans under normal conditions. Moreover, SOD@EXO improved the resistance against heat and oxidative stress, leading to notable survival ratio under these hostile conditions. Overall, the exosome-mediated delivery of SOD could reduce ROS level and delay aging in C. elegans model, thereby providing potential strategies to treat ROS-related diseases in future.

REVIEWS/COMMENTS/ METHODS/EDITORIALS

Defining a longevity biotechnology company

Nicola Boekstein ✉, Nir Barzilai, André Bertram, Joe Betts-LaCroix, Kristen Fortney, Stephen B. Helliwell,

Michael Hufford, Joan Mannick, Jerry McLaughlin, Jim Mellon, Eric Morgen, Nils Regge, Daisy A. Robinton,

David A. Sinclair, Sergey Young, Risa Starr, Alex Zhavoronkov & James Peyer

The meaning of adaptation in aging: insights from cellular senescence, epigenetic clocks and stem cell alterations

Mikolaj Ogrodnik ✉ & Vadim N. Gladyshev ✉

Abstract

With recent rapid progress in research on aging, there is increasing evidence that many features commonly considered to be mechanisms or drivers of aging in fact represent adaptations. Here, we examine several such features, including cellular senescence, epigenetic aging and stem cell alterations. We draw a distinction between the causes and consequences of aging and define short-term consequences as 'responses' and long-term ones as 'adaptations'. We also discuss 'damaging adaptations', which despite having beneficial effects in the short term, lead to exacerbation of the initial insult and acceleration of aging. Features commonly recognized as 'basic mechanisms of the aging process' are critically examined for the possibility of their adaptation-driven emergence from processes such as cell competition and the wound-like features of the aging body. Finally, we speculate on the meaning of these interactions for the aging process and their relevance for the development of antiaging interventions.

What do we mean by "aging"? Questions and perspectives revealed by studies in Drosophila

Andrew P K Wodrich [1], Andrew W Scott [2], Edward Giniger [3]

Affiliations + expand
PMID: 37354919   DOI: 10.1016/j.mad.2023.111839

Abstract

What is the nature of aging, and how best can we study it? Here, using a series of questions that highlight differing perspectives about the nature of aging, we ask how data from Drosophila melanogaster at the organismal, tissue, cellular, and molecular levels shed light on the complex interactions among the phenotypes associated with aging. Should aging be viewed as an individual's increasing probability of mortality over time or as a progression of physiological states? Are all age-correlated changes in physiology detrimental to vigor or are some compensatory changes that maintain vigor? Why do different age-correlated functions seem to change at different rates in a single individual as it ages? Should aging be considered as a single, integrated process across the scales of biological resolution, from organismal to molecular, or must we consider each level of biological scale as a separate, distinct entity? Viewing aging from these differing perspectives yields distinct but complementary interpretations about the properties and mechanisms of aging and may offer a path through the complexities related to understanding the nature of aging.

Aging – What it is and how to measure it

Maryam Keshavarz [a], Kan Xie [a], Daniele Bano [b], Dan Ehninger [a]

The current understanding of the biology of aging is largely based on research aimed at identifying factors that influence lifespan. However, lifespan as a sole proxy measure of aging has limitations because it can be influenced by specific pathologies (not generalized physiological deterioration in old age). Hence, there is a great need to discuss and design experimental approaches that are well-suited for studies targeting the biology of aging, rather than the biology of specific pathologies that restrict the lifespan of a given species. For this purpose, we here review various perspectives on aging, discuss agreement and disagreement among researchers on the definition of aging, and show that while slightly different aspects are emphasized, a widely accepted feature, shared across many definitions, is that aging is accompanied by phenotypic changes that occur in a population over the course of an average lifespan. We then discuss experimental approaches that are in line with these considerations, including multidimensional analytical frameworks as well as designs that facilitate the proper assessment of intervention effects on aging rate. The proposed framework can guide discovery approaches to aging mechanisms in all key model organisms (e.g., mouse, fish models, D. melanogaster, C. elegans) as well as in humans.

Biomarkers selection and mathematical modeling in biological age estimation

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PMID: 37393295   DOI: 10.1038/s41514-023-00110-8

Abstract

Biological age (BA) is important for clinical monitoring and preventing aging-related disorders and disabilities. Clinical and/or cellular biomarkers are measured and integrated in years using mathematical models to display an individual's BA. To date, there is not yet a single or set of biomarker(s) and technique(s) that is validated as providing the BA that reflects the best real aging status of individuals. Herein, a comprehensive overview of aging biomarkers is provided and the potential of genetic variations as proxy indicators of the aging state is highlighted. A comprehensive overview of BA estimation methods is also provided as well as a discussion of their performances, advantages, limitations, and potential approaches to overcome these limitations.

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Biomarkers of ageing: Current state-of-art, challenges, and opportunities

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Given the unprecedented phenomenon of population ageing, studies have increasing captured the heterogeneity within the ageing process. In this context, the concept of "biological age" has been introduced as an integrated measure reflecting the individualized ageing pace. Identifying reliable and robust biomarkers of age is critical for the accurate risk stratification of individuals and exploration into antiageing interventions. Numerous potential biomarkers of ageing have been proposed, spanning from molecular changes and imaging characteristics to clinical phenotypes. In this review, we will start off with a discussion of the development of ageing biomarkers, then we will provide a comprehensive summary of currently identified ageing biomarkers in humans, discuss the rationale behind each biomarker and highlight their accuracy and clinical value with a contemporary perspective. Additionally, we will discuss the challenges, potential applications, and future opportunities in this field. While research on ageing biomarkers has led to significant progress and applications, further investigations are still necessary. We anticipate that future breakthroughs in this field will involve exploring potential mechanisms, developing biomarkers by combining various data sources or employing new technologies, and validating the clinical value of existing and emerging biomarkers through comprehensive collaboration and longitudinal studies.

Drugs Targeting Mechanisms of Aging to Delay Age-Related Disease and Promote Healthspan: Proceedings of a National Institute on Aging Workshop

Sara E Espinoza [1] [2], Sundeep Khosla [3], Joseph A Baur [4], Rafael de Cabo [5], Nicolas Musi [6]

The geroscience hypothesis posits that by targeting key hallmarks of aging we may simultaneously prevent or delay several age-related diseases and thereby increase healthspan, or life span spent free of significant disease and disability. Studies are underway to examine several possible pharmacological interventions for this purpose. As part of a National Institute on Aging workshop on the development of function-promoting therapies, scientific content experts provided literature reviews and state-of-the-field assessments for the studies of senolytics, nicotinamide adenine dinucleotide (NAD+) boosters, and metformin. Cellular senescence increases with age, and preclinical studies demonstrate that the use of senolytic drugs improves healthspan in rodents. Human studies using senolytics are in progress. NAD+ and its phosphorylated form, NADP+, play vital roles in metabolism and cellular signaling. Increasing NAD+ by supplementation with precursors including nicotinamide riboside and nicotinamide mononucleotide appears to extend healthspan in model organisms, but human studies are limited and results are mixed. Metformin is a biguanide widely used for glucose lowering, which is believed to have pleiotropic effects targeting several hallmarks of aging. Preclinical studies suggest it improves life span and healthspan, and observational studies suggest benefits for the prevention of several age-related diseases. Clinical trials are underway to examine metformin for healthspan and frailty prevention. Preclinical and emerging clinical studies suggest there is potential to improve healthspan through the use of pharmacologic agents reviewed. However, much further research is needed to demonstrate benefits and general safety for wider use, the appropriate target populations, and longer-term outcomes.

Going beyond established model systems of Alzheimer's disease: companion animals provide novel insights into the neurobiology of aging

Alexandra A. de Sousa, Brier A. Rigby Dames, Emily C. Graff, Rania Mohamedelhassan, Tatianna Vassilopoulos & Christine J. Charvet ✉

Alzheimer's disease (AD) is characterized by brain plaques, tangles, and cognitive impairment. AD is one of the most common age-related dementias in humans. Progress in characterizing AD and other age-related disorders is hindered by a perceived dearth of animal models that naturally reproduce diseases observed in humans. Mice and nonhuman primates are model systems used to understand human diseases. Still, these model systems lack many of the biological characteristics of Alzheimer-like diseases (e.g., plaques, tangles) as they grow older. In contrast, companion animal models (cats and dogs) age in ways that resemble humans. Both companion animal models and humans show evidence of brain atrophy, plaques, and tangles, as well as cognitive decline with age. We embrace a One Health perspective, which recognizes that the health of humans is connected to those of animals, and we illustrate how such a perspective can work synergistically to enhance human and animal health. A comparative biology perspective is ideally suited to integrate insights across veterinary and human medical disciplines and solve long-standing problems in aging.

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Clinical relevance of animal models in aging-related dementia research

Pranesh Padmanabhan [1], Jürgen Götz [2]

Affiliations + expand

Abstract

Alzheimer's disease (AD) and other, less prevalent dementias are complex age-related disorders that exhibit multiple etiologies. Over the past decades, animal models have provided pathomechanistic insight and evaluated countless therapeutics; however, their value is increasingly being questioned due to the long history of drug failures. In this Perspective, we dispute this criticism. First, the utility of the models is limited by their design, as neither the etiology of AD nor whether interventions should occur at a cellular or network level is fully understood. Second, we highlight unmet challenges shared between animals and humans, including impeded drug transport across the blood-brain barrier, limiting effective treatment development. Third, alternative human-derived models also suffer from the limitations mentioned above and can only act as complementary resources. Finally, age being the strongest AD risk factor should be better incorporated into the experimental design, with computational modeling expected to enhance the value of animal models.

Amyloid formation as a protein phase transition

Thomas C. T. Michaels ✉, Daoyuan Qian, Anđela Šarić, Michele Vendruscolo, Sara Linse & Tuomas P. J. Knowles ✉

Abstract

The formation of amyloid fibrils is a general class of protein self-assembly behaviour, which is associated with both functional biology and the development of a number of disorders, such as Alzheimer and Parkinson diseases. In this Review, we discuss how general physical concepts from the study of phase transitions can be used to illuminate the fundamental mechanisms of amyloid self-assembly. We summarize progress in the efforts to describe the essential biophysical features of amyloid self-assembly as a nucleation-and-growth process and discuss how master equation approaches can reveal the key molecular pathways underlying this process, including the role of secondary nucleation. Additionally, we outline how non-classical aspects of aggregate formation involving oligomers or biomolecular condensates have emerged, inspiring developments in understanding, modelling and modulating complex protein assembly pathways. Finally, we consider how these concepts can be applied to kinetics-based drug discovery and therapeutic design to develop treatments for protein aggregation diseases.

Considerations for reproducible omics in aging research

Param Priya Singh ✉ & Bérénice A. Benayoun ✉

Abstract

Technical advancements over the past two decades have enabled the measurement of the panoply of molecules of cells and tissues including transcriptomes, epigenomes, metabolomes and proteomes at unprecedented resolution. Unbiased profiling of these molecular landscapes in the context of aging can reveal important details about mechanisms underlying age-related functional decline and age-related diseases. However, the high-throughput nature of these experiments creates unique analytical and design demands for robustness and reproducibility. In addition, 'omic' experiments are generally onerous, making it crucial to effectively design them to eliminate as many spurious sources of variation as possible as well as account for any biological or technical parameter that may influence such measures. In this Perspective, we provide general guidelines on best practices in the design and analysis of omic experiments in aging research from experimental design to data analysis and considerations for long-term reproducibility and validation of such studies.

The circadian clock and extracellular matrix homeostasis in aging and age-related diseases

Michal Dudek, Joe Swift, and Qing-Jun Meng ✉ ⓘ

The extracellular matrix (ECM) is the noncellular scaffolding component present within all tissues and organs. It provides crucial biochemical and biomechanical cues to instruct cellular behavior and has been shown to be under circadian clock regulation, a highly conserved cell-intrinsic timekeeping mechanism that has evolved with the 24-hour rhythmic environment. Aging is a major risk factor for many diseases, including cancer, fibrosis, and neurodegenerative disorders. Both aging and our modern 24/7 society disrupt circadian rhythms, which could contribute to altered ECM homeostasis. Understanding the daily dynamics of ECM and how this mechanism changes with age will have a profound impact on tissue health, disease prevention, and improving treatments. Maintaining rhythmic oscillations has been proposed as a hallmark of health. On the other hand, many hallmarks of aging turn out to be key regulators of circadian timekeeping mechanisms. In this review, we summarize new work linking the ECM with circadian clocks and tissue aging. We discuss how the changes in the biomechanical and biochemical properties of ECM during aging may contribute to circadian clock dysregulation. We also consider how the dampening of clocks with age could compromise the daily dynamic regulation of ECM homeostasis in matrix-rich tissues. This review aims to encourage new concepts and testable hypotheses about the two-way interactions between circadian clocks and ECM in the context of aging.

Chronic inflammation and the hallmarks of aging

Jordan J. Baechle [1 8], Nan Chen [2 6 8], Priya Makhijani [1 5], Shawn Winer [2], David Furman [1 3 4 8] ✉, Daniel A. Winer [1 2 5 6 7 8] ✉

Recently, the hallmarks of aging were updated to include dysbiosis, disabled macroautophagy, and chronic inflammation. In particular, the low-grade chronic inflammation during aging, without overt infection, is defined as "inflammaging," which is associated with increased morbidity and mortality in the aging population. Emerging evidence suggests a bidirectional and cyclical relationship between chronic inflammation and the development of age-related conditions, such as cardiovascular diseases, neurodegeneration, cancer, and frailty. How the crosstalk between chronic inflammation and other hallmarks of aging underlies biological mechanisms of aging and age-related disease is thus of particular interest to the current geroscience research.

Age-associated anatomical and physiological alterations in Caenorhabditis elegans

Emmanuel Spanoudakis [1], Nektarios Tavernarakis [2]

Affiliations + expand

Abstract

Since its introduction by Sydney Brenner, Caenorhabditis elegans has become a widely studied organism. Given its highly significant properties, including transparency, short lifespan, self-fertilization, high reproductive yield and ease in manipulation and genetic modifications, the nematode has contributed to the elucidation of several fundamental aspects of biology, such as development and ageing. Moreover, it has been extensively used as a platform for the modelling of ageing-associated human disorders, especially those related to neurodegeneration. The use of C. elegans for such purposes requires, and at the same time promotes the investigation of its normal ageing process. In this review we aim to summarize the major organismal alterations during normal worm ageing, in terms of morphology and functionality.

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