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Life Biosciences Presents Groundbreaking Data at ARVO Demonstrating Restoration of Visual Function in Nonhuman Primates

Data in a nonhuman primate model of Non-arteritic Anterior Ischemic Optic Neuropathy (NAION) demonstrates the ability to restore visual function after delivery of a novel gene therapy

BOSTON, April 23, 2023 — Life Biosciences, a biotechnology company advancing innovative cellular rejuvenation technologies to reverse diseases of aging and injury and ultimately restore health for patients, today announced preclinical data in nonhuman primates (NHP) for its novel gene therapy candidate which uses a partial epigenetic reprogramming approach to restore visual function.

This approach has been shown to reverse aging, improve vision, and extend lifespan in mice, but whether epigenetic reprogramming would work in primates was not known. Today, researchers at Life Bio and academic researchers, including Dr. Bruce Ksander and Dr. David Sinclair, reported that Life Bio's therapy significantly restored visual function in an NHP model of non-arteritic anterior ischemic optic neuropathy (NAION), a disorder similar to a stroke of the eye that is characterized by painless yet sudden loss of vision. The data, presented at the Association for Research in Vision and Ophthalmology (ARVO) 2023 conference in New Orleans, LA, represents an important step forward toward enabling human clinical trials to potentially treat a variety of ophthalmic disorders and other diseases of aging.

Life Bio's lead platform reprograms the epigenome of older animals to resemble that of younger animals via expression of three Yamanaka factors, Oct4, Sox2, and Klf4, collectively known as OSK. The approach partially reprograms cells to resemble a more youthful state while retaining their original cellular identity. Previous data from Life Bio and academic researchers, which were also presented at ARVO 2023, have shown that treatment with OSK reverses retinal aging and restores vision in old mice in a mouse model of glaucoma. Now, with the data presented today at ARVO, the company has demonstrated restoration of visual function and increased nerve axon survival in an NHP model that mimics human NAION deficits in retinal ganglion cells. Key data highlights include the following:

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‘De overheid zal het steeds moeilijker krijgen om de pensioenen te betalen’: zo leg je het best een spaarpot aan

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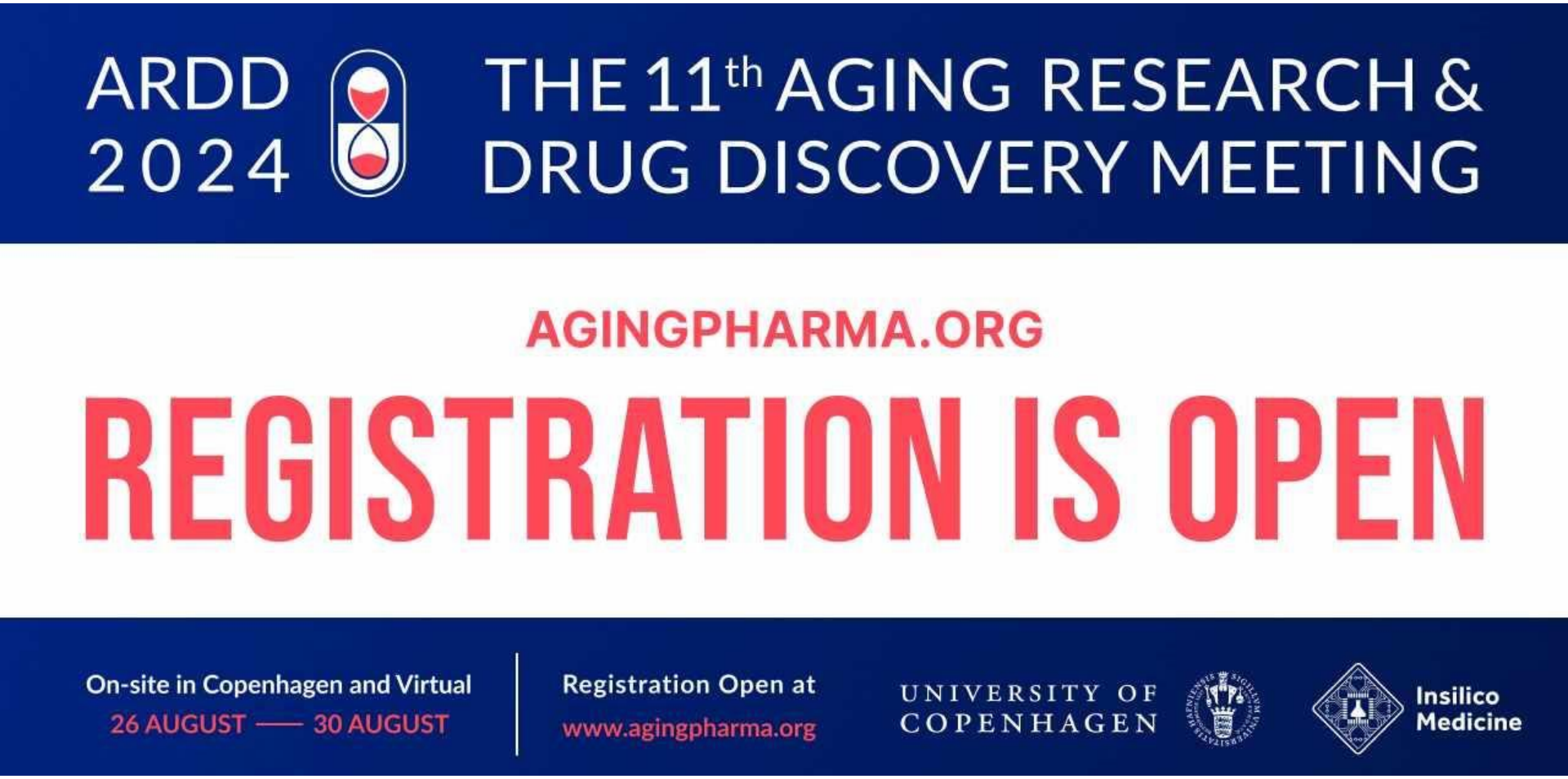

Aging research articles

TERT activation targets DNA methylation and multiple aging hallmarks

Insufficient telomerase activity, stemming from low *telomerase reverse transcriptase* (*TERT*) gene transcription, contributes to telomere dysfunction and aging pathologies. Besides its traditional function in telomere synthesis, TERT acts as a transcriptional co-regulator of genes pivotal in aging and age-associated diseases. Here, we report the identification of a TERT activator compound (TAC) that upregulates *TERT* transcription via the MEK/ERK/AP-1 cascade. In primary human cells and naturally aged mice, TAC-induced elevation of TERT levels promotes telomere synthesis, blunts tissue aging hallmarks with reduced cellular senescence and inflammatory cytokines, and silences $p16^{INK4a}$ expression via upregulation of DNMT3B-mediated promoter hypermethylation. In the brain, TAC alleviates neuroinflammation, increases neurotrophic factors, stimulates adult neurogenesis, and preserves cognitive function without evident toxicity, including cancer risk. Together, these findings underscore TERT's critical role in aging processes and provide preclinical proof of concept for physiological TERT activation as a strategy to mitigate multiple aging hallmarks and associated pathologies.

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PREPRINT

Telomerase RNA component knockout exacerbates *S. aureus* pneumonia by extensive inflammation and dysfunction of T cells

Yasmina Reisser, Franziska Hornung, Antje Haeder, Thurid Lauf, Sandor Nietzsche, Bettina Löffler, Stefanie Deinhardt-Emmer

The telomerase RNA component (Terc) constitutes a non-coding RNA critical for telomerase function, commonly associated with aging and pivotal in immunomodulation during inflammation. Our study unveils heightened susceptibility to pneumonia caused by *Staphylococcus aureus* (*S. aureus* in *Terc* knockout ($Terc^{ko/ko}$) mice compared to both young and old infected counterparts. The exacerbated infection in $Terc^{ko/ko}$ mice correlates with heightened inflammation, manifested by elevated interleukin-1β (IL-1β) levels and activation of the NLR Family Pyrin Domain Containing 3 (NLRP3) inflammasome within the lung. Employing mRNA sequencing methods alongside *in vitro* analysis of alveolar macrophages (AMs) and T cells, our study elucidates a compelling correlation between $Terc^{ko/ko}$, inflammation, and impaired T cell functionality. Terc deletion results in compromised T cell function, characterized by dysregulation of the T cell receptor and absence of CD247, potentially compromising the host's capacity to mount an effective immune response against *S. aureus*. This investigation provides insights into the intricate mechanisms governing increased vulnerability to severe pneumonia in the context of Terc deficiency, which might also contribute to aging-related pathologies, while also revealing for the first time the influence of Terc on T cell function.

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SGLT2 inhibition eliminates senescent cells and alleviates pathological aging

It has been reported that accumulation of senescent cells in various tissues contributes to pathological aging and that elimination of senescent cells (senolysis) improves age-associated pathologies. Here, we demonstrate that inhibition of sodium–glucose co-transporter 2 (SGLT2) enhances clearance of senescent cells, thereby ameliorating age-associated phenotypic changes. In a mouse model of dietary obesity, short-term treatment with the SGLT2 inhibitor canagliflozin reduced the senescence load in visceral adipose tissue and improved adipose tissue inflammation and metabolic dysfunction, but normalization of plasma glucose by insulin treatment had no effect on senescent cells. Canagliflozin extended the lifespan of mice with premature aging even when treatment was started in middle age. Metabolomic analyses revealed that short-term treatment with canagliflozin upregulated 5-aminoimidazole-4-carboxamide-1-β-D-ribofuranoside, enhancing immune-mediated clearance of senescent cells by downregulating expression of programmed cell death-ligand 1. These findings suggest that inhibition of SGLT2 has an indirect senolytic effect by enhancing endogenous immunosurveillance of senescent cells.

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PREPRINT

Multiomics mapping and characterization of cellular senescence in aging human skeletal muscle uncovers a novel senotherapeutic for sarcopenia

Cellular senescence is recognized as a hallmark of organismal aging but how it drives aging particularly in human tissues is not fully understood, partly due to the complex heterogeneous nature of senescence. Here in this study, we leverage single-nucleus multiomics to profile senescence in mononucleated cells of human skeletal muscle and provide the first senescence atlas. We demonstrate the intra- and inter-populational transcriptomic and epigenomic heterogeneity and dynamics of senescence in the cells. We also identify commonalities and variations in senescence-associated secretory phenotypes (SASPs) among the cells and elucidate the function of SASPs in mediating cellular interactions and niche deregulation. Furthermore, we identify targetable SASP factors and demonstrate the possibility of using Maraviroc as a pharmacological senotherapeutic for treating age-associated sarcopenia in muscle. Lastly, we define transcription factors that govern senescence state and SASP induction in aging muscle and elucidate the key function and the underlying mechanism of JUNB in regulating SASP activation in senescent cells. Altogether, our findings demonstrate the prevalence and function of cellular senescence in skeletal muscle and identify a novel pharmacological intervention for sarcopenia.

Senolytic effects of exercise in human muscles require acute inflammation

Higher intensity exercise, despite causing more tissue damage, improved aging conditions. We previously observed decreased $p16^{INK4a}$ mRNA in human skeletal muscle after high-intensity interval exercise (HIIE), with no change following equivalent work in moderate-intensity continuous exercise. This raises the question of whether the observed senolytic effect of exercise is mediated by inflammation, an immune response induced by muscle damage. In this study, inflammation was blocked using a multiple dose of ibuprofen (total dose: 1200 mg), a commonly consumed nonsteroidal anti-inflammatory drug (NSAID), in a placebo-controlled, counterbalanced crossover trial. Twelve men aged 20–26 consumed ibuprofen or placebo before and after HIIE at 120% maximum aerobic power. Multiple muscle biopsies were taken for tissue analysis before and after HIIE. $p16^{INK4a+}$ cells were located surrounding myofibers in muscle tissues. The maximum decrease in $p16^{INK4a}$ mRNA levels within muscle tissues occurred at 3 h post-exercise (−82%, $p < 0.01$), gradually recovering over the next 3–24 h. A concurrent reduction pattern in CD11b mRNA (−87%, $p < 0.01$) was also found within the same time frame. Ibuprofen treatment attenuated the post-exercise reduction in both $p16^{INK4a}$ mRNA and CD11b mRNA. The strong correlation ($r = 0.88$, $p < 0.01$) between $p16^{INK4a}$ mRNA and CD11b mRNA in muscle tissues suggests a connection between the markers of tissue aging and pro-inflammatory myeloid differentiation. In conclusion, our results suggest that the senolytic effect of high-intensity exercise on human skeletal muscle is mediated by acute inflammation.

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SenNet recommendations for detecting senescent cells in different tissues

Once considered a tissue culture-specific phenomenon, cellular senescence has now been linked to various biological processes with both beneficial and detrimental roles in humans, rodents and other species. Much of our understanding of senescent cell biology still originates from tissue culture studies, where each cell in the culture is driven to an irreversible cell cycle arrest. By contrast, in tissues, these cells are relatively rare and difficult to characterize, and it is now established that fully differentiated, postmitotic cells can also acquire a senescence phenotype. The SenNet Biomarkers Working Group was formed to provide recommendations for the use of cellular senescence markers to identify and characterize senescent cells in tissues. Here, we provide recommendations for detecting senescent cells in different tissues based on a comprehensive analysis of existing literature reporting senescence markers in 14 tissues in mice and humans. We discuss some of the recent advances in detecting and characterizing cellular senescence, including molecular senescence signatures and morphological features, and the use of circulating markers. We aim for this work to be a valuable resource for both seasoned investigators in senescence-related studies and newcomers to the field.

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Lens capsule advanced glycation end products induce senescence in epithelial cells: Implications for secondary cataracts

Grace Cooksley, Mi-Hyun Nam, Rooban B. Nahomi, Johanna Rankenberg, Andrew J. O. Smith, Yvette M. Wormstone, I. Michael Wormstone, Ram H. Nagaraj

Posterior capsule opacification (PCO) is a common complication after cataract surgery. Residual lens epithelial cells (LECs) on the anterior lens capsule, after cataract surgery, migrate to the posterior lens capsule and undergo transdifferentiation into myofibroblast-like cells. Those cells synthesize excessive amounts of extracellular matrix and contribute to fibrosis during PCO. Cellular senescence, a phenomenon that increases with aging, has been implicated in several fibrotic diseases. Here, we have investigated the prevalence of senescent LECs within the lens posterior capsule and the ability of advanced glycation end products (AGEs) in lens capsules to induce senescence, contributing to PCO. Aged lens capsules from pseudophakic human cadaver eyes showed the presence of senescent LECs. In human capsular bags, LECs showed an age-dependent increase in senescence after 28 days of culture. Human LECs cultured on aged lens capsules for 3 days underwent senescence; this effect was not seen in LECs cultured on young lens capsules. Human LECs cultured on an AGE-modified extracellular matrix (ECM-AGEs) showed an AGE-concentration-dependent increase in the expression of senescence markers and reactive oxygen species (ROS) levels. Treatment with a RAGE antagonist and ROS inhibitor reduced the expression of senescence and fibrotic markers. Additionally, conditioned media from ECM-AGEs-treated cells induced the expression of fibrotic markers in naïve LECs. Together, these suggest that AGEs in the capsule induce senescence of LECs, which triggers the mesenchymal transition of neighboring non-senescent LECs and contributes to PCO.

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PREPRINT

Exosomes Released from Senescent Cells and Circulatory Exosomes Isolated from Human Plasma Reveal Aging-associated Proteomic and Lipid Signatures

Sandip Kumar Patel, Joanna Bons, Jacob P. Rose, Jessie R. Chappel, Rebecca L. Beres, Mark A. Watson, Corey Webster, Jordan B. Burton, Roland Bruderer, Pierre-Yves Desprez, Lukas Reiter, Judith Campisi, Erin S. Baker, Birgit Schilling

Senescence emerged as a significant mechanism of aging and age-related diseases, offering an attractive target for clinical interventions. Senescent cells release a senescence-associated secretory phenotype (SASP), including exosomes that may act as signal transducers between distal tissues, propagating secondary or bystander senescence and signaling throughout the body. However, the composition of exosome SASP remains underexplored, presenting an opportunity for novel unbiased discovery. Here, we present a detailed proteomic and lipidomic analysis of exosome SASP using mass spectrometry from human plasma from young and older individuals and from tissue culture of senescent primary human lung fibroblasts. We identified ~1,300 exosome proteins released by senescent fibroblasts induced by three different senescence inducers causing most exosome proteins to be differentially regulated with senescence. In parallel, a human plasma cohort from young and old individuals revealed over 1,350 exosome proteins and 171 plasma exosome proteins were regulated when comparing old vs young individuals. Of the age-regulated plasma exosome proteins, we observed 52 exosome SASP factors that were also regulated in exosomes from the senescent fibroblasts, including serine protease inhibitors (SERPINs), Prothrombin, Coagulation factor V, Plasminogen, and Reelin. In addition, 247 lipids were identified with high confidence in all exosome samples. Following the senescence inducers, a majority of the identified phosphatidylcholine, phosphatidylethanolamine, and sphingomyelin species increased significantly indicating cellular membrane changes. The most notable categories of significantly changed proteins were related to extracellular matrix remodeling and inflammation, both potentially detrimental pathways that can damage surrounding tissues and even induce secondary or bystander senescence. Our findings reveal mechanistic insights and potential senescence biomarkers, enabling a better approach to surveilling the senescence burden in the aging population and offering promising therapeutic targets for interventions.

The impact of astrocytic NF−κB on healthy and Alzheimer's disease brains

Astrocytes play a role in healthy cognitive function and Alzheimer's disease (AD). The transcriptional factor nuclear factor-κB (NF-κB) drives astrocyte diversity, but the mechanisms are not fully understood. By combining studies in human brains and animal models and selectively manipulating NF-κB function in astrocytes, we deepened the understanding of the role of astrocytic NF-κB in brain health and AD. In silico analysis of bulk and cell-specific transcriptomic data revealed the association of NF-κB and astrocytes in AD. Confocal studies validated the higher level of p50 NF-κB and phosphorylated-p65 NF-κB in glial fibrillary acidic protein $(GFAP)^{+}$-astrocytes in AD versus non-AD subjects. In the healthy mouse brain, chronic activation of astrocytic NF-κB disturbed the proteomic milieu, causing a loss of mitochondrial-associated proteins and the rise of inflammatory-related proteins. Sustained NF-κB signaling also led to microglial reactivity, production of pro-inflammatory mediators, and buildup of senescence-related protein $p16^{INK4A}$ in neurons. However, in an AD mouse model, NF-κB inhibition accelerated β-amyloid and tau accumulation. Molecular biology studies revealed that astrocytic NF-κB activation drives the increase in GFAP and inflammatory proteins and aquaporin-4, a glymphatic system protein that assists in mitigating AD. Our investigation uncovered fundamental mechanisms by which NF-κB enables astrocytes' neuroprotective and neurotoxic responses in the brain.

Therapeutic effects of a novel synthetic α-secretase

Sung Bin Kim [1], Bo-Ram Mun [2], Sung Yoon Kim [1], Muthukumar Elangovan [1], Euy Jun Park [1], Won-Seok Choi [2], Woo Jin Park [1]

Excessive accumulation of amyloid-β (Aβ) has been associated with the pathogenesis of Alzheimer's disease (AD). Clinical studies have further proven that elimination of Aβ can be a viable therapeutic option. In the current study, we conceptualized a fusion membrane protein, referred to as synthetic α-secretase (SAS), that can cleave amyloid precursor protein (APP) and Aβ specifically at the α-site. In mammalian cells, SAS indeed cleaved APP and Aβ at the α-site. Overexpression of SAS in the hippocampus was achieved by direct injection of recombinant adeno-associated virus serotype 9 (AAV9) that expresses SAS (AAV9-SAS) into the bilateral ventricles of mouse brains. SAS enhanced the non-amyloidogenic processing of APP, thus reducing the levels of soluble Aβ and plaques in the 5xFAD mice. In addition, SAS significantly attenuated the cognitive deficits in 5xFAD mice, as demonstrated by novel object recognition and Morris water maze tests. Unlike other Aβ-cleaving proteases, SAS has highly strict substrate specificity. We propose that SAS can be an efficient modality to eliminate excessive Aβ from diseased brains.

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Transcriptome analysis of cynomolgus macaques throughout their lifespan reveals age-related immune patterns

Hyeon-Mu Cho, Se-Hee Choe, Ja-Rang Lee, Hye-Ri Park, Min-Gyeong Ko, Yun-Jung Lee, Hwal-Yong Lee, Sung Hyun Park, Sang-Je Park, Young-Hyun Kim & Jae-Won Huh

Despite the different perspectives by diverse research sectors spanning several decades, aging research remains uncharted territory for human beings. Therefore, we investigated the transcriptomic characteristics of eight male healthy cynomolgus macaques, and the annual sampling was designed with two individuals in four age groups. As a laboratory animal, the macaques were meticulously shielded from all environmental factors except aging. The results showed recent findings of certain immune response and the age-associated network of primate immunity. Three important aging patterns were identified and each gene clusters represented a different immune response. The increased expression pattern was predominantly associated with innate immune cells, such as Neutrophils and NK cells, causing chronic inflammation with aging whereas the other two decreased patterns were associated with adaptive immunity, especially "B cell activation" affecting antibody diversity of aging. Furthermore, the hub gene network of the patterns reflected transcriptomic age and correlated with human illness status, aiding in future human disease prediction. Our macaque transcriptome profiling results offer systematic insights into the age-related immunological features of primates.

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The genetic architecture of biological age in nine human organ systems

Junhao Wen ✉, Ye Ella Tian, Ioanna Skampardoni, Zhijian Yang, Yuhan Cui, Filippos Anagnostakis, Elizabeth Mamourian, Bingxin Zhao, Arthur W. Toga, Andrew Zalesky & Christos Davatzikos

Investigating the genetic underpinnings of human aging is essential for unraveling the etiology of and developing actionable therapies for chronic diseases. Here, we characterize the genetic architecture of the biological age gap (BAG; the difference between machine learning-predicted age and chronological age) across nine human organ systems in 377,028 participants of European ancestry from the UK Biobank. The BAGs were computed using cross-validated support vector machines, incorporating imaging, physical traits and physiological measures. We identify 393 genomic loci–BAG pairs ($P < 5 \times 10^{-8}$) linked to the brain, eye, cardiovascular, hepatic, immune, metabolic, musculoskeletal, pulmonary and renal systems. Genetic variants associated with the nine BAGs are predominantly specific to the respective organ system (organ specificity) while exerting pleiotropic links with other organ systems (interorgan cross-talk). We find that genetic correlation between the nine BAGs mirrors their phenotypic correlation. Further, a multiorgan causal network established from two-sample Mendelian randomization and latent causal variance models revealed potential causality between chronic diseases (for example, Alzheimer's disease and diabetes), modifiable lifestyle factors (for example, sleep duration and body weight) and multiple BAGs. Our results illustrate the potential for improving human organ health via a multiorgan network, including lifestyle interventions and drug repurposing strategies.

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Caloric restriction reduces trabecular bone loss during aging and improves bone marrow adipocyte endocrine function in male mice

Introduction: Caloric restriction (CR) is a nutritional intervention that increases life expectancy while lowering the risk for cardio-metabolic disease. Its effects on bone health, however, remain controversial. For instance, CR has been linked to increased accumulation of bone marrow adipose tissue (BMAT) in long bones, a process thought to elicit detrimental effects on bone. Qualitative differences have been reported in BMAT in relation to its specific anatomical localization, subdividing it into physiological and potentially pathological BMAT. We here examine the local impact of CR on bone composition, microstructure and its endocrine profile in the context of aging.

Methods: Young and aged male C57Bl6J mice were subjected to CR for 8 weeks and were compared to age-matched littermates with free food access. We assessed bone microstructure and BMAT by micro-CT, bone fatty acid and transcriptomic profiles, and bone healing.

Results: CR increased tibial BMAT accumulation and adipogenic gene expression. CR also resulted in elevated fatty acid desaturation in the proximal and mid-shaft regions of the tibia, thus more closely resembling the biochemical lipid profile of the distally located, physiological BMAT. In aged mice, CR attenuated trabecular bone loss, suggesting that CR may revert some aspects of age-related bone dysfunction. Cortical bone, however, was decreased in young mice on CR and remained reduced in aged mice, irrespective of dietary intervention. No negative effects of CR on bone regeneration were evident in either young or aged mice.

Discussion: Our findings indicate that the timing of CR is critical and may exert detrimental effects on bone biology if administered during a phase of active skeletal growth. Conversely, CR exerts positive effects on trabecular bone structure in the context of aging, which occurs despite substantial accumulation of BMAT. These data suggest that the endocrine profile of BMAT, rather than its fatty acid composition, contributes to healthy bone maintenance in aged mice.

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Suppressed basal mitophagy drives cellular aging phenotypes that can be reversed by a p62-targeting small molecule

Selective degradation of damaged mitochondria by autophagy (mitophagy) is proposed to play an important role in cellular homeostasis. However, the molecular mechanisms and the requirement of mitochondrial quality control by mitophagy for cellular physiology are poorly understood. Here, we demonstrated that primary human cells maintain highly active basal mitophagy initiated by mitochondrial superoxide signaling. Mitophagy was found to be mediated by PINK1/Parkin-dependent pathway involving p62 as a selective autophagy receptor (SAR). Importantly, this pathway was suppressed upon the induction of cellular senescence and in naturally aged cells, leading to a robust shutdown of mitophagy. Inhibition of mitophagy in proliferating cells was sufficient to trigger the senescence program, while reactivation of mitophagy was necessary for the anti-senescence effects of NAD precursors or rapamycin. Furthermore, reactivation of mitophagy by a p62-targeting small molecule rescued markers of cellular aging, which establishes mitochondrial quality control as a promising target for anti-aging interventions.

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PREPRINT

Long-Term NMN Treatment Increases Lifespan and Healthspan in Mice in a Sex Dependent Manner

Nicotinamide adenine dinucleotide (NAD) is essential for many enzymatic reactions, including those involved in energy metabolism, DNA repair and the activity of sirtuins, a family of defensive deacylases. During aging, levels of NAD+ can decrease by up to 50% in some tissues, the repletion of which provides a range of health benefits in both mice and humans. Whether or not the NAD+ precursor nicotinamide mononucleotide (NMN) extends lifespan in mammals is not known. Here we investigate the effect of long-term administration of NMN on the health, cancer burden, frailty and lifespan of male and female mice. Without increasing tumor counts or severity in any tissue, NMN treatment of males and females increased activity, maintained more youthful gene expression patterns, and reduced overall frailty. Reduced frailty with NMN treatment was associated with increases in levels of Anerotruncus colihominis, a gut bacterium associated with lower inflammation in mice and increased longevity in humans. NMN slowed the accumulation of adipose tissue later in life and improved metabolic health in male but not female mice, while in females but not males, NMN increased median lifespan by 8.5%, possible due to sex-specific effects of NMN on NAD+ metabolism. Together, these data show that chronic NMN treatment delays frailty, alters the microbiome, improves male metabolic health, and increases female mouse lifespan, without increasing cancer burden. These results highlight the potential of NAD+ boosters for treating age-related conditions and the importance of using both sexes for interventional lifespan studies.

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Epigenetic predictors of species maximum life span and other life-history traits in mammals

By analyzing 15,000 samples from 348 mammalian species, we derive DNA methylation (DNAm) predictors of maximum life span (R = 0.89), gestation time (R = 0.96), and age at sexual maturity (R = 0.85). Our maximum life-span predictor indicates a potential innate longevity advantage for females over males in 17 mammalian species including humans. The DNAm maximum life-span predictions are not affected by caloric restriction or partial reprogramming. Genetic disruptions in the somatotropic axis such as growth hormone receptors have an impact on DNAm maximum life span only in select tissues. Cancer mortality rates show no correlation with our epigenetic estimates of life-history traits. The DNAm maximum life-span predictor does not detect variation in life span between individuals of the same species, such as between the breeds of dogs. Maximum life span is determined in part by an epigenetic signature that is an intrinsic species property and is distinct from the signatures that relate to individual mortality risk.

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PREPRINT

Immunomodulatory Role of the Stem Cell Circadian Clock in Muscle Repair

Pei Zhu, Eric M Pfrender, Adam W T Steffeck, Colleen R Reczek, Yalu Zhou, Abhishek Vijay Thakkar, Neha R Gupta, Amber Willbanks, Richard L Lieber, Ishan Roy, Navdeep S Chandel, Clara B Peek

The circadian clock orchestrates vital physiological processes such as metabolism, immune function, and tissue regeneration, aligning them with the optimal time of day. This study identifies an intricate interplay between the circadian clock within muscle stem cells (SCs) and their capacity to modulate the immune microenvironment during muscle regeneration. We uncover that the SC clock provokes time of day-dependent induction of inflammatory response genes following injury, particularly those related to neutrophil activity and chemotaxis. These responses are driven by rhythms of cytosolic regeneration of the signaling metabolite NAD^+. We demonstrate that genetically enhancing cytosolic NAD^+ regeneration in SCs is sufficient to induce robust inflammatory responses that significantly influence muscle regeneration. Furthermore, using mononuclear single-cell sequencing of the regenerating muscle niche, we uncover a key role for the cytokine CCL2 in mediating SC-neutrophil crosstalk in a time of day-dependent manner. Our findings highlight a crucial intersection between SC metabolic shifts and immune responses within the muscle microenvironment, dictated by the circadian rhythms, and underscore the potential for targeting circadian and metabolic pathways to enhance tissue regeneration.

The effect of dose, frequency, and timing of protein supplementation on muscle mass in older adults: A systematic review and meta-analysis

Protein supplementation has shown to improve muscle mass in older adults. However, its effect may be influenced by supplementation dose, frequency and timing. This systematic review aimed to assess the effect of dose, frequency and timing of protein supplementation on muscle mass in older adults. Five databases were systematically searched from inception to 14 March 2023, for randomised controlled trials investigating the effect of protein supplementation on muscle mass in adults aged ≥65 years. Random effects meta-analyses were performed, stratified by population. Subgroups were created for dose (≥30 g, <30 g/day), frequency (once, twice, three times/day) and timing of supplementation (at breakfast, breakfast and lunch, breakfast and dinner, all meals, between meals). Heterogeneity within and between subgroups was assessed using I^2 and Cochran Q statistics respectively. Thirty-eight articles were included describing community-dwelling (28 articles, n=3204, 74.6±3.4 years, 62.8 % female), hospitalised (8 articles, n=590, 77.0±3.7 years, 50.3 % female) and institutionalised populations (2 articles, n=156, 85.7±1.2 years, 71.2 % female). Protein supplementation showed a positive effect on muscle mass in community-dwelling older adults (standardised mean difference 0.116; 95 % confidence interval 0.032–0.200 kg, p=0.007, I^2=15.3 %) but the effect did not differ between subgroups of dose, frequency and timing (Q=0.056, 0.569 and 3.084 respectively, p>0.05). Data including hospitalised and institutionalised populations were limited. Protein supplementation improves muscle mass in community-dwelling older adults, but its dose, frequency or timing does not significantly influence the effect.

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Comprehensive analysis of gene signatures associated with aging in human aortic dissection

Background: Aortic dissection (AD) is a lethal aortic disease with limited effective therapeutic strategies. Aging increases the risk of AD, yet the underlying mechanisms remain unclear. This study aims to analyze the association of aging-related genes (Args) and AD using bioinformatic analysis. This helps provide novel insights into AD pathogenesis and contributes to developing novel therapeutic strategies.

Methods: mRNA (GSE52093, GSE153434), miRNA (GSE98770) and single-cell RNA-sequencing (scRNA-seq, GSE213740) datasets of AD were downloaded from GEO database. Args were downloaded from Aging Atlas database. Differentially-expressed Args were determined by intersecting Args and differentially-expressed mRNAs of two mRNA datasets. Cytoscape was used to identify hub genes and construct hub gene regulatory networks related to miRNAs. Seurat and clusterProfiler R package were used for investigating expression patterns of hub genes at single-cell level, and functional analysis, respectively. To validate the cellular expression pattern of hub genes, the same analysis was applied to our own scRNA-seq data. Drugs targeting hub Args were determined using the DGIdb database.

Results: HGF, *CXCL8*, *SERPINE1*, *HIF1A*, *TIMP1*, *ESR1* and *PLAUR* were identified as aging-related hub genes in AD. miR-221-3p was predicted to interact with *ESR1*. A decreased *ESR1* expression in smooth muscle cell subpopulation 4 (SMC4) was observed in AD versus normal aortic tissues, which was validated by sequencing 197,605 aortic cells from 13 AD patients. Additionally, upregulated genes of SMC4 in AD tissues were enriched in the "cellular senescence" pathway. These data indicated that decreased *ESR1* might promote SMC4 aging during AD formation. Eleven existing drugs targeting hub genes were identified, including ruxolitinib and filgrastim, which are associated with AD.

Conclusions: By sequencing transcriptomic data, this study revealed aging-related hub genes and regulatory network involved in AD formation. Additionally, this study proposed a noteworthy hypothesis that downregulated *ESR1* may exacerbate AD by promoting SMC aging, which requires further investigation.

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Intersection of Aging and Particulate Matter 2.5 Exposure in Real World: Effects on Inflammation and Endocrine Axis Activities in Rats

Exposure to particulate matter 2.5 (PM2.5) is detrimental to multiple organ systems. Given the factor that aging also alters the cellularity and response of immune system and dysfunction of hypothalamic-pituitary-adrenal, -gonad and -thyroid axes, it is imperative to investigate whether chronic exposure to PM2.5 interacts with aging in these aspects. In this study, two-months-old Sprague-Dawley rats were exposed to real world PM2.5 for 16 months. PM2.5 exposure diminished the relative numbers of $CD4^+$ T cells and $CD8^+$ T cells and increased the relative number of B cells in the peripheral blood of male rats. Conversely, only reduced relative number of $CD4^+$ T cells was seen in the blood of female rats. These shifts resulted in elevated levels of proinflammatory factors interleukin-6 and tumor necrosis factor-α in the circulatory systems of both sex, with females also evidencing a rise in interleukin-1β levels. Moreover, heightened interleukin-6 was solely discernible in the hippocampus of female subjects, while increased tumor necrosis factor-α concentrations were widespread in female brain regions but confined to the male hypothalamus. Notable hormonal decreases were observed following PM2.5 exposure in both sex. These comprised declines in biomolecules such as corticotrophin-releasing hormone and cortisol, generated by the hypothalamic-pituitary-adrenal axis, and thyroid-releasing hormone and triiodothyronine, produced by the hypothalamic-pituitary-thyroid axis. Hormonal elements such as gonadotropin-releasing hormone, luteinizing hormone, and follicle-stimulating hormone, derived from the hypothalamic-pituitary-gonad axis, were also diminished. Exclusive to male rats was a reduction in adrenocorticotropic hormone levels, whereas a fall in thyroid-stimulating hormone was unique to female rats. Decreases in sex-specific hormones, including testosterone, estradiol, and progesterone, were also noted. These findings significantly enrich our comprehension of the potential long-term health repercussions associated with PM2.5 interaction particularly among the aging populace.

C. elegans aging research

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PREPRINT

Comprehensive evaluation of lifespan-extending molecules in *C. elegans*

Grace B. Phelps, Jonas Morin, Carla Pinto, Lucas Schoenfeldt, Sebastien Guilmot, Alejandro Ocampo, Kevin Perez

The nematode *C. elegans* has long served as a gold-standard model organism in aging research, particularly since the discovery of long-lived mutants in conserved aging pathways including daf-2 (IGF1) and age-1 (PI3K). Its short lifespan and small size make it highly suitable for high throughput experiments. While numerous molecules have been tested for their effects on *C. elegans* lifespan, consensus is still lacking regarding the most effective and reproducible compounds. Confounding effects, especially those related to drug-bacteria interactions, remain a contentious issue in the literature. In this study, we evaluated 16 of the most frequently reported lifespan-extending molecules in *C. elegans*, examining their effects on lifespan with two different diets (live and UV-killed OP50). In addition, we assessed the compounds' impact on bacterial growth, their effects on various nematode strains, and the impact of the starting age of treatment. Our findings first confirmed robust lifespan extension with many, but not all, of the 16 tested compounds from the literature, and revealed that some of them could be combined to get synergistic effects. Additionally, we showed that some of these compounds also extend lifespan in the fly *D. melanogaster*, demonstrating a conserved effect across species. Finally, by expanding our screen to a broader pool of molecules, we identified novel lifespan-extending compounds in *C. elegans*.

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PREPRINT

Multiple Targets, One Goal: Compounding life-extending effects through Polypharmacology

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Analysis of lifespan-extending compounds suggested the most effective geroprotectors target multiple biogenic amine receptors. To test this hypothesis, we used graph neural networks to predict such polypharmacological compounds and evaluated them in *C. elegans*. Over 70% of the selected compounds extended lifespan, with effect sizes in the top 5% compared to the DrugAge database. This reveals that rationally designing polypharmacological compounds enables the design of geroprotectors with exceptional efficacy.

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Systematic mapping of organism-scale gene-regulatory networks in aging using population asynchrony

In aging, physiologic networks decline in function at rates that differ between individuals, producing a wide distribution of lifespan. Though 70% of human lifespan variance remains unexplained by heritable factors, little is known about the intrinsic sources of physiologic heterogeneity in aging. To understand how complex physiologic networks generate lifespan variation, new methods are needed. Here, we present Asynch-seq, an approach that uses gene-expression heterogeneity within isogenic populations to study the processes generating lifespan variation. By collecting thousands of single-individual transcriptomes, we capture the Caenorhabditis elegans "pan-transcriptome"-a highly resolved atlas of non-genetic variation. We use our atlas to guide a large-scale perturbation screen that identifies the decoupling of total mRNA content between germline and soma as the largest source of physiologic heterogeneity in aging, driven by pleiotropic genes whose knockdown dramatically reduces lifespan variance. Our work demonstrates how systematic mapping of physiologic heterogeneity can be applied to reduce inter-individual disparities in aging.

Aging atlas reveals cell-type-specific effects of pro-longevity strategies

Shihong Max Gao, Yanyan Qi, Qinghao Zhang, Youchen Guan, Yi-Tang Lee, Lang Ding, Lihua Wang, Aaron S. Mohammed, Hongjie Li, Yusi Fu & Meng C. Wang

Organismal aging involves functional declines in both somatic and reproductive tissues. Multiple strategies have been discovered to extend lifespan across species. However, how age-related molecular changes differ among various tissues and how those lifespan-extending strategies slow tissue aging in distinct manners remain unclear. Here we generated the transcriptomic Cell Atlas of Worm Aging (CAWA, http://mengwanglab.org/atlas) of wild-type and long-lived strains. We discovered cell-specific, age-related molecular and functional signatures across all somatic and germ cell types. We developed transcriptomic aging clocks for different tissues and quantitatively determined how three different pro-longevity strategies slow tissue aging distinctively. Furthermore, through genome-wide profiling of alternative polyadenylation (APA) events in different tissues, we discovered cell-type-specific APA changes during aging and revealed how these changes are differentially affected by the pro-longevity strategies. Together, this study offers fundamental molecular insights into both somatic and reproductive aging and provides a valuable resource for in-depth understanding of the diversity of pro-longevity mechanisms.

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Full-length direct RNA sequencing reveals extensive remodeling of RNA expression, processing and modification in aging Caenorhabditis elegans

Erin C Schiksnis, Ian A Nicastro, Amy E Pasquinelli

Organismal aging is marked by decline in cellular function and anatomy, ultimately resulting in death. To inform our understanding of the mechanisms underlying this degeneration, we performed standard RNA sequencing and Nanopore direct RNA sequencing over an adult time course in Caenorhabditis elegans. Long reads allowed for identification of hundreds of novel isoforms and age-associated differential isoform accumulation, resulting from alternative splicing and terminal exon choice. Genome-wide analysis reveals a decline in RNA processing fidelity and a rise in inosine and pseudouridine editing events in transcripts from older animals. In this first map of pseudouridine modifications for C. elegans, we find that they largely reside in coding sequences and that the number of genes with this modification increases with age. Collectively, this analysis discovers transcriptomic signatures associated with age and is a valuable resource to understand the many processes that dictate altered gene expression patterns and post-transcriptional regulation in aging.

Improved resilience and proteostasis mediate longevity upon DAF-2 degradation in old age

Little is known about the possibility of reversing age-related biological changes when they have already occurred. To explore this, we have characterized the effects of reducing insulin/IGF-1 signaling (IIS) during old age. Reduction of IIS throughout life slows age-related decline in diverse species, most strikingly in the nematode Caenorhabditis elegans. Here we show that even at advanced ages, auxin-induced degradation of DAF-2 in single tissues, including neurons and the intestine, is still able to markedly increase C. elegans lifespan. We describe how reversibility varies among senescent changes. While senescent pathologies that develop in mid-life were not reversed, there was a rejuvenation of the proteostasis network, manifesting as a restoration of the capacity to eliminate otherwise intractable protein aggregates that accumulate with age. Moreover, resistance to several stressors was restored. These results support several new conclusions. (1) Loss of resilience is not solely a consequence of pathologies that develop in earlier life. (2) Restoration of proteostasis and resilience by inhibiting IIS is a plausible cause of the increase in lifespan. And (3), most interestingly, some aspects of the age-related transition from resilience to frailty can be reversed to a certain extent. This raises the possibility that the effect of IIS and related pathways on resilience and frailty during aging in higher animals might possess some degree of reversibility.

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Measuring chemical changes during aging in vivo with stimulated Raman scattering microscopy

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Abstract

Aging related biological mechanisms are often difficult to probe in situ without exogenous fluorophores. Here, we leverage label-free stimulated Raman scattering (SRS) microscopy to provide new insights into aging in C. elegans. We demonstrate multispectral SRS imaging of whole worms in vivo with quantitative chemical insights across different ages. We show that both lipid and protein synthesis and compartmentalization are associated with aging in worms. We additionally use SRS in combination with simultaneous two-photon fluorescence imaging to characterize the putatively aberrant protein accumulation. Moreover, we observe notable SRS image differences when worms are subjected to calorie restriction, suggesting a promising avenue towards understanding calorie-restriction's enhancing effects on longevity when coupled to proteomic and metabolomic analysis.

REVIEWS/COMMENTS/ METHODS/EDITORIALS

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PERSPECTIVE | CELL BIOLOGY

Cellular senescence in normal physiology

Long associated with aging, senescent cells can promote health and have physiological roles

JOÃO PEDRO DE MAGALHÃES Authors Info & Affiliations

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Regulation of cell function and identity by cellular senescence

Anda Huna, Amélie Massemin, Gabriela Makulyte, Jean-Michel Flaman, Nadine Martin, David Bernard

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During aging and in some contexts, like embryonic development, wound healing, and diseases such as cancer, senescent cells accumulate and play a key role in different pathophysiological functions. A long-held belief was that cellular senescence decreased normal cell functions, given the loss of proliferation of senescent cells. This view radically changed following the discovery of the senescence-associated secretory phenotype (SASP), factors released by senescent cells into their microenvironment. There is now accumulating evidence that cellular senescence also promotes gain-of-function effects by establishing, reinforcing, or changing cell identity, which can have a beneficial or deleterious impact on pathophysiology. These effects may involve both proliferation arrest and autocrine SASP production, although they largely remain to be defined. Here, we provide a historical overview of the first studies on senescence and an insight into emerging trends regarding the effects of senescence on cell identity.

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Senescent cell–derived vaccines: a new concept towards an immune response against cancer and aging?

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Affiliations + expand

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Free article

Abstract

Two recent seminal works have untangled the intricate role of tumor-associated senescent cells in cancer progression, or regression, by guiding our immune system against cancer cells. The characterization of these unique, yet diverse cell populations, should be considered, particularly when contemplating the use of senolytics, which are drugs that selectively eliminate senescent cells, in a cancer framework. Here, we will describe the current knowledge in this field. In particular, we will discuss how the presence of senescent cells in tumors could be used as a therapeutic target in immunogenic cancers and how we may hypothetically design an adaptive anti-aging vaccine.

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The impact of COVID-19 on "biological aging"

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Abstract

The global impact of the SARS-CoV-2 pandemic has been unprecedented, posing a significant public health challenge. Chronological age has been identified as a key determinant for severe outcomes associated with SARS-CoV-2 infection. Epigenetic age acceleration has previously been observed in various diseases including human immunodeficiency virus (HIV), Cytomegalovirus (CMV), cardiovascular diseases, and cancer. However, a comprehensive review of this topic is still missing in the field. In this review, we explore and summarize the research work focusing on biological aging markers, i.e., epigenetic age and telomere attrition in COVID-19 patients. From the reviewed articles, we identified a consistent pattern of epigenetic age dysregulation and shortened telomere length, revealing the impact of COVID-19 on epigenetic aging and telomere attrition.

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Long COVID as a Disease of Accelerated Biological Aging: An Opportunity to Translate Geroscience Interventions

Areez Shafqat [a], Mary Clare Masters [b], Utkarsh Tripathi [c], Tamara Tchkonia [c d], James L. Kirkland [c d e], Shahrukh K. Hashmi [e f g]

It has been four years since long COVID—the protracted consequences that survivors of COVID-19 face—was first described. Yet, this entity continues to devastate the quality of life of an increasing number of COVID-19 survivors without any approved therapy. Furthermore, there remains a paucity of clinical trials addressing the biological root causes of this disease. Notably, the symptoms of long COVID—including but not limited to exercise intolerance, cognitive impairment, orthostasis, and functional decline—are typically seen with advancing age. Leveraging this similarity, we posit that Geroscience—which aims to target the biological drivers of aging to prevent age-associated conditions as a group—could offer promising therapeutic avenues for long COVID. Bearing this in mind, this review presents a framework for studying long COVID as a state of effectively accelerated biological aging. Thus, we comprehensively review here the role of biological hallmarks of aging in long COVID, identifying research gaps and proposing directions for future preclinical and clinical studies.

Lost in translation: challenges of current pharmacotherapy for sarcopenia

Shih-Yin Tsai [1]

A healthy lifespan relies on independent living, in which active skeletal muscle is a critical element. The cost of not recognizing and acting earlier on unhealthy or aging muscle could be detrimental, since muscular weakness is inversely associated with all-cause mortality. Sarcopenia is characterized by a decline in skeletal muscle mass and strength and is associated with aging. Exercise is the only effective therapy to delay sarcopenia development and improve muscle health in older adults. Although numerous interventions have been proposed to reduce sarcopenia, none has yet succeeded in clinical trials. This review evaluates the biological gap between recent clinical trials targeting sarcopenia and the preclinical studies on which they are based, and suggests an alternative approach to bridge the discrepancy.

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Computational modeling of aging-related gene networks: a review

The aging process is a complex and multifaceted phenomenon affecting all living organisms. It involves a gradual deterioration of tissue and cellular function, leading to a higher risk of developing various age-related diseases (ARDs), including cancer, neurodegenerative, and cardiovascular diseases. The gene regulatory networks (GRNs) and their respective niches are crucial in determining the aging rate. Unveiling these GRNs holds promise for developing novel therapies and diagnostic tools to enhance healthspan and longevity. This review examines GRN modeling approaches in aging, encompassing differential equations, Boolean/fuzzy logic decision trees, Bayesian networks, mutual information, and regression clustering. These approaches provide nuanced insights into the intricate gene-protein interactions in aging, unveiling potential therapeutic targets and ARD biomarkers. Nevertheless, outstanding challenges persist, demanding more comprehensive datasets and advanced algorithms to comprehend and predict GRN behavior accurately. Despite these hurdles, identifying GRNs associated with aging bears immense potential and is poised to transform our comprehension of human health and aging. This review aspires to stimulate further research in aging, fostering the innovation of computational approaches for promoting healthspan and longevity.

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The chemical language of protein glycation

Meghan S. Martin, Jeremiah W. Jacob-Dolan, Vo Tri Tin Pham, Nicole M. Sjoblom & Rebecca A. Scheck

Glycation is a non-enzymatic post-translational modification (PTM) that is correlated with many diseases, including diabetes, cancer and age-related disorders. Although recent work points to the importance of glycation as a functional PTM, it remains an open question whether glycation has a causal role in cellular signaling and/or disease development. In this Review, we contextualize glycation as a specific mechanism of carbon stress and consolidate what is known about advanced glycation end-product (AGE) structures and mechanisms. We highlight the current understanding of glycation as a PTM, focusing on mechanisms for installing, removing or recognizing AGEs. Finally, we discuss challenges that have hampered a more complete understanding of the biological consequences of glycation. The development of tools for predicting, modulating, mimicking or capturing glycation will be essential for interpreting a post-translational glycation network. Therefore, continued insights into the chemistry of glycation will be necessary to advance understanding of glycation biology.

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Interplay of Proteostasis Capacity and Protein Aggregation: Implications for Cellular Function and Disease

Mark S. Hipp [1 2 3], F. Ulrich Hartl [4 5 6]

Eukaryotic cells are equipped with an intricate proteostasis network (PN), comprising nearly 3,000 components dedicated to preserving proteome integrity and sustaining protein homeostasis. This protective system is particularly important under conditions of external and intrinsic cell stress, where inherently dynamic proteins may unfold and lose functionality. A decline in proteostasis capacity is associated with the aging process, resulting in a reduced folding efficiency of newly synthesized proteins and a deficit in the cellular capacity to degrade misfolded proteins. A critical consequence of PN insufficiency is the accumulation of cytotoxic protein aggregates that underlie various age-related neurodegenerative conditions and other pathologies. By interfering with specific proteostasis components, toxic aggregates place an excessive burden on the PN's ability to maintain proteome integrity. This initiates a feed-forward loop, wherein the generation of misfolded and aggregated proteins ultimately leads to proteostasis collapse and cellular demise.

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SIRT1 signaling pathways in sarcopenia: Novel mechanisms and potential therapeutic targets

Sarcopenia is an aging-related skeletal disease characterized by decreased muscle mass, strength, and physical function, severely affecting the quality of life (QoL) of the elderly population. Sirtuin 1 (SIRT1), as a nicotinamide adenine dinucleotide (NAD+)-dependent histone deacetylases, has been reported to participate in various aging-related signaling pathways and exert protective effect on many human diseases. SIRT1 functioned as an important role in the occurrence and progression of sarcopenia through regulating key pathways related to protein homeostasis, apoptosis, mitochondrial dysfunction, insulin resistance and autophagy in skeletal muscle, including SIRT1/Forkhead Box O (FoxO), AMP-activated protein kinase (AMPK)/SIRT1/nuclear factor κB (NF-κB), SIRT1/p53, AMPK/SIRT1/peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α), and SIRT1/live kinase B1 (LKB1)/AMPK pathways. However, the specific mechanisms of these processes have not been fully illuminated. Currently, several SIRT1-mediated interventions on sarcopenia have been preliminarily developed, such as SIRT1 activator polyphenolic compounds, exercising and calorie restriction. In this review, we summarized the predominant mechanisms of SIRT1 involved in sarcopenia and therapeutic modalities targeting the SIRT1 signaling pathways for the prevention and prognosis of sarcopenia.

Decoding sTREM2: its impact on Alzheimer's disease – a comprehensive review of mechanisms and implications

Cui Lin [1], Yu Kong [1], Qian Chen [1], Jixiang Zeng [2], Xiaojin Pan [1], Jifei Miao [1]

Soluble Triggering Receptor Expressed on Myeloid Cells 2 (sTREM2) plays a crucial role in the pathogenesis of Alzheimer's disease (AD). This review comprehensively examines sTREM2's involvement in AD, focusing on its regulatory functions in microglial responses, neuroinflammation, and interactions with key pathological processes. We discuss the dynamic changes in sTREM2 levels in cerebrospinal fluid and plasma throughout AD progression, highlighting its potential as a therapeutic target. Furthermore, we explore the impact of genetic variants on sTREM2 expression and its interplay with other AD risk genes. The evidence presented in this review suggests that modulating sTREM2 activity could influence AD trajectory, making it a promising avenue for future research and drug development. By providing a holistic understanding of sTREM2's multifaceted role in AD, this review aims to guide future studies and inspire novel therapeutic strategies.

Repurposing effect of cardiovascular–metabolic drug to increase lifespan: a systematic review of animal studies and current clinical trial progress

With the increase in life expectancy, aging has emerged as a significant health concern. Due to its various mechanisms of action, cardiometabolic drugs are often repurposed for other indications, including aging. This systematic review analyzed and highlighted the repositioning potential of cardiometabolic drugs to increase lifespan as an aging parameter in animal studies and supplemented by information from current clinical trial registries. Systematic searching in animal studies was performed based on PICO: "animal," "cardiometabolic drug," and "lifespan." All clinical trial registries were also searched from the WHO International Clinical Trial Registry Platform (ICTRP). Analysis of 49 animal trials and 10 clinical trial registries show that various cardiovascular and metabolic drugs have the potential to target lifespan. Metformin, acarbose, and aspirin are the three most studied drugs in animal trials. Aspirin and acarbose are the promising ones, whereas metformin exhibits various results. In clinical trial registries, metformin, omega-3 fatty acid, acarbose, and atorvastatin are currently cardiometabolic drugs that are repurposed to target aging. Published clinical trial results show great potential for omega-3 and metformin in healthspan. **Systematic Review Registration:** crd.york.ac.uk/prospero/display_record.php?RecordID=457358, identifier: CRD42023457358.

OTHER RESEARCH & REVIEWS

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Brainwide silencing of prion protein by AAV-mediated delivery of an engineered compact epigenetic editor

RESULTS

To address these challenges, we engineered a compact, enzyme-free epigenetic editor termed CHARM (Coupled Histone tail for Autoinhibition Release of Methyltransferase). Through a direct fusion with the histone H3 tail and a noncatalytic Dnmt3l domain, CHARM is able to recruit and activate DNA methyltransferases endogenously expressed in the cell to methylate the target gene. CHARM can act independently of KRAB transcriptional repression domains and is compatible with multiple DNA-binding modalities, including CRISPR-Cas, transcription activator–like effectors, and zinc finger proteins. The small size of zinc finger proteins enables up to three DNA targeting elements to be accommodated in a single AAV with additional room for regulatory elements to confer cell-type specificity. When coupled to a prion protein–targeting zinc finger domain and delivered to the mouse brain through AAV, CHARM methylates the prion gene promoter and achieves up to 80% brainwide reduction in neuronal prion protein, far exceeding the minimal reduction required for therapeutic benefit. Furthermore, we developed self-silencing CHARMs that autonomously deactivate themselves after silencing their target. This approach temporally limits CHARM expression to circumvent potential antigenicity and off-target activity resulting from chronic expression in nondividing neurons.