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Sven Bulterijs

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Analysts 'highly encouraged' by TREM2 reduction seen in Vigil's phase 1 Alzheimer's data

By **Nick Paul Taylor** · Jan 23, 2025 9:51am

Upcoming conferences

Upcoming conferences

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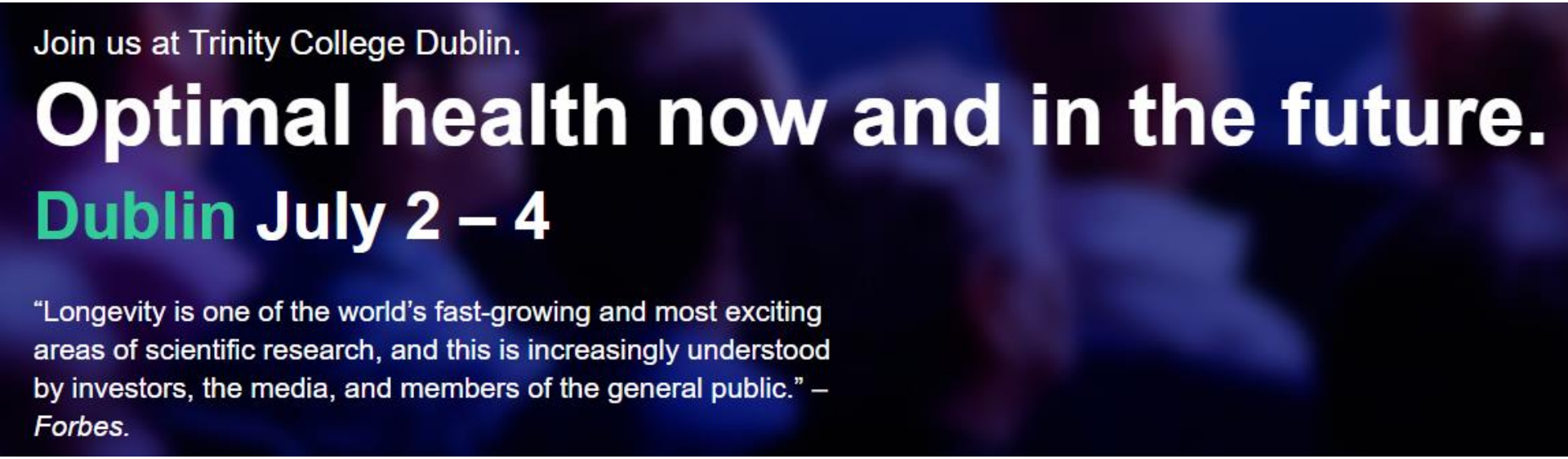

Aging research articles

Plasma protein-based organ-specific aging and mortality models unveil diseases as accelerated aging of organismal systems

Ludger J.E. Goeminne [1,4] · Anastasiya Vladimirova [1,4] · Alec Eames [1,4] · … · Kejun Ying [1,4] · Mahdi Moqri [1,4] · Vadim N. Gladyshev [1,4,5] … Show more

Aging is a complex process manifesting at molecular, cellular, organ, and organismal levels. It leads to functional decline, disease, and ultimately death, but the relationship between these fundamental biomedical features remains elusive. By applying elastic net regularization to plasma proteome data of over 50,000 human subjects in the UK Biobank and other cohorts, we report interpretable organ-specific and conventional aging models trained on chronological age, mortality, and longitudinal proteome data. These models predict organ/system-specific disease and indicate that men age faster than women in most organs. Accelerated organ aging leads to diseases in these organs, and specific diets, lifestyles, professions, and medications influence organ aging rates. We then identify proteins driving these associations with organ-specific aging. Our analyses reveal that age-related chronic diseases epitomize accelerated organ- and system-specific aging, modifiable through environmental factors, advocating for both universal whole-organism and personalized organ/system-specific anti-aging interventions.

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Cross-tissue comparison of epigenetic aging clocks in humans

Abner T. Apsley, Qiaofeng Ye, Avshalom Caspi, Christopher Chiaro, Laura Etzel, Waylon J. Hastings, Christine M. Heim, John Kozlosky, Jennie G. Noll, Hannah M. C. Schreier ... See all authors

Epigenetic clocks are a common group of tools used to measure biological aging—the progressive deterioration of cells, tissues, and organs. Epigenetic clocks have been trained almost exclusively using blood-based tissues, but there is growing interest in estimating epigenetic age using less-invasive oral-based tissues (i.e., buccal or saliva) in both research and commercial settings. However, differentiated cell types across body tissues exhibit unique DNA methylation landscapes and age-related alterations to the DNA methylome. Applying epigenetic clocks derived from blood-based tissues to estimate epigenetic age of oral-based tissues may introduce biases. We tested the within-person comparability of common epigenetic clocks across five tissue types: buccal epithelial, saliva, dry blood spots, buffy coat (i.e., leukocytes), and peripheral blood mononuclear cells. We tested 284 distinct tissue samples from 83 individuals aged 9–70 years. Overall, there were significant within-person differences in epigenetic clock estimates from oral-based versus blood-based tissues, with average differences of almost 30 years observed in some age clocks. In addition, most epigenetic clock estimates of blood-based tissues exhibited low correlation with estimates from oral-based tissues despite controlling for cellular proportions and other technical factors. Notably, the Skin and Blood clock exhibited the greatest concordance across all tissue types, indicating its unique ability to estimate chronological age in oral- and blood-based tissues. Our findings indicate that application of blood-derived epigenetic clocks in oral-based tissues may not yield comparable estimates of epigenetic age, highlighting the need for careful consideration of tissue type when estimating epigenetic age.

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Somatic mutation as an explanation for epigenetic aging

Zane Koch, Adam Li, Daniel S. Evans, Steven Cummings ✉ & Trey Ideker ✉

DNA methylation marks have recently been used to build models known as epigenetic clocks, which predict calendar age. As methylation of cytosine promotes C-to-T mutations, we hypothesized that the methylation changes observed with age should reflect the accrual of somatic mutations, and the two should yield analogous aging estimates. In an analysis of multimodal data from 9,331 human individuals, we found that CpG mutations indeed coincide with changes in methylation, not only at the mutated site but with pervasive remodeling of the methylome out to ±10 kilobases. This one-to-many mapping allows mutation-based predictions of age that agree with epigenetic clocks, including which individuals are aging more rapidly or slowly than expected. Moreover, genomic loci where mutations accumulate with age also tend to have methylation patterns that are especially predictive of age. These results suggest a close coupling between the accumulation of sporadic somatic mutations and the widespread changes in methylation observed over the course of life.

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Slowed epigenetic aging in Olympic champions compared to non-champions

The lifestyle patterns of top athletes are highly disciplined, featuring strict exercise regimens, nutrition plans, and mental preparation, often beginning at a young age. Recently, it was shown that physically active individuals exhibit slowed epigenetic aging and better age-related outcomes. Here, we investigate whether the extreme intensity of physical activity of Olympic champions still has a beneficial effect on epigenetic aging. To test this hypothesis, we examined the epigenetic aging of 59 Hungarian Olympic champions and of the 332 control subjects, 205 were master rowers. We observed that Olympic champions exhibit slower epigenetic aging, applying seven state-of-the-art epigenetic aging clocks. Additionally, male champions who won any medal within the last 10 years showed slower epigenetic aging compared to other male champions, while female champions exhibited the opposite trend. We also found that wrestlers had higher age acceleration compared to gymnasts, fencers, and water polo players. We identified the top 20 genes that showed the most remarkable difference in promoter methylation between Olympic champions and non-champions. The hypo-methylated genes are involved in synaptic health, glycosylation, metal ion membrane transfer, and force generation. Most of the hyper-methylated genes were associated with cancer promotion. The data suggest that rigorous and long-term exercise from adolescence to adulthood has beneficial effects on epigenetic aging.

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Longitudinal serum proteome mapping reveals biomarkers for healthy ageing and related cardiometabolic diseases

The blood proteome contains biomarkers of ageing and age-associated diseases, but such markers are rarely validated longitudinally. Here we map the longitudinal proteome in 7,565 serum samples from a cohort of 3,796 middle-aged and elderly adults across three time points over a 9-year follow-up period. We pinpoint 86 ageing-related proteins that exhibit signatures associated with 32 clinical traits and the incidence of 14 major ageing-related chronic diseases. Leveraging a machine-learning model, we pick 22 of these proteins to generate a proteomic healthy ageing score (PHAS), capable of predicting the incidence of cardiometabolic diseases. We further identify the gut microbiota as a modifiable factor influencing the PHAS. Our data constitute a valuable resource and offer useful insights into the roles of serum proteins in ageing and age-associated cardiometabolic diseases, providing potential targets for intervention with therapeutics to promote healthy ageing.

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PREPRINT

Age and Sex-Specific Changes in Mitochondrial Quality Control in Skeletal and Cardiac Muscle

Skeletal and cardiac muscle mitochondria exist in a dynamic reticulum that is maintained by a balance of mitochondrial biogenesis, fusion, fission, and mitophagy. This balance is crucial for adequate ATP production, and alterations in skeletal muscle mitochondria have been implicated in aging-associated declines in mitochondrial function. We sought to determine whether age and biological sex affect mitochondrial content [Complex IV (CIV)], biogenesis (PGC-1α), fusion (MFN2, OPA1), fission (DRP1, FIS1), and mitophagy (Parkin, Pink1) markers in skeletal and cardiac muscle by assessing protein expression in tibialis anterior (TA) and ventricular tissue from 16 young (≤6 months) and 16 old (≥20 months) male and female Sprague-Dawley rats. In the TA, CIV expression was 40% lower in old vs. young rats ($p<0.001$), indicating lower mitochondrial content, and coincided with higher expression of Parkin (+4-fold, $p<0.001$). Further, MFN2 expression was higher (+2-fold, $p<0.005$) and Parkin was lower (-40%, $p=0.014$) in older rats. In cardiac muscle, mitochondrial content was maintained in old vs. young rats, and this occurred concomitantly with higher expression of both PGC-1α and Parkin. MFN2 and OPA1 expression were also 1.2-5-fold higher in older rats ($p<0.05$ for all). Largely, protein expression did not differ between male and female rats, with the exception of Pink1 and FIS1 expression in the TA. Collectively, older skeletal and cardiac muscle demonstrated higher expression of fusion and mitophagy proteins, which indicates age alters the balance of biogenesis, fission, fusion, and mitophagy. This may, in turn, affect the ability to provide ATP to these metabolically active tissues.

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PREPRINT

Altered relaxation and Mitochondria-Endoplasmic Reticulum Contacts Precede Major (Mal)adaptaions in Aging Skeletal Muscle and are Prevented by Exercise

Sarcopenia, or age-related muscle dysfunction, contributes to morbidity and mortality. Besides decreases in muscle force, sarcopenia is associated with atrophy and fast-to-slow fiber type switching, which is typically secondary to denervation in humans and rodents. However, very little is known about cellular changes preceding these important (mal)adaptations. To this matter, mitochondria and the sarcoplasmic reticulum are critical for tension generation in myofibers. They physically interact at the boundaries of sarcomeres forming subcellular hubs called mitochondria-endo/sarcoplasmic reticulum contacts (MERCs). Yet, whether changes at MERCs ultrastructure and proteome occur early in aging is unknown. Here, studying young adult and older mice we reveal that aging slows muscle relaxation leading to longer excitation-contraction-relaxation (ECR) cycles before maximal force decreases and fast-to-slow fiber switching takes place. We reveal that muscle MERC ultrastructure and mitochondria-associated ER membrane (MAM) protein composition are also affected early in aging and are closely associated with rate of muscle relaxation. Additionally, we demonstrate that regular exercise preserves muscle relaxation rate and MERC ultrastructure in early aging. Finally, we profile a set of muscle MAM proteins involved in energy metabolism, protein quality control, Ca^{2+} homeostasis, cytoskeleton integrity and redox balance that are inversely regulated early in aging and by exercise. These may represent new targets to preserve muscle function in aging individuals.

Unravelling the transcriptomic symphony of muscle ageing: key pathways and hub genes altered by ageing and caloric restriction in rat muscle revealed by RNA sequencing

Age-related muscle wasting, sarcopenia is an extensive loss of muscle mass and strength with age and a major cause of disability and accidents in the elderly. Mechanisms purported to be involved in muscle ageing and sarcopenia are numerous but poorly understood, necessitating deeper study. Hence, we employed high-throughput RNA sequencing to survey the global changes in protein-coding gene expression occurring in skeletal muscle with age. Caloric restriction (CR) is a known prophylactic intervention against sarcopenia. Therefore, total RNA was isolated from the muscle tissue of both rats fed ad libitum and CR rats. RNA-seq data were subjected to Gene Ontology, pathway, co-expression, and interaction network analyses. This revealed the functional pathways most activated by both ageing and CR, as well as the key "hub" proteins involved in their activation.RNA-seq revealed 442 protein-coding genes to be upregulated and 377 to be downregulated in aged muscle, compared to young muscle. Upregulated genes were commonly involved in protein folding and immune responses; meanwhile, downregulated genes were often related to developmental biology. CR was found to suppress 69.7% and rescue 57.8% of the genes found to be upregulated and downregulated in aged muscle, respectively. In addition, CR uniquely upregulated 291 and downregulated 304 protein-coding genes. Hub genes implicated in both ageing and CR included Gc, Plg, Irf7, Ifit3, Usp18, Rsad2, Blm and RT1-A2, whilst those exclusively implicated in CR responses included Alb, Apoa1, Ambp, F2, Apoh, Orm1, Mx1, Oasl2 and Rtp4. Hub genes involved in ageing but unaffected by CR included Fgg, Fga, Fgb and Serpinc1. In conclusion, this comprehensive RNA sequencing study highlights gene expression patterns, hub genes and signalling pathways most affected by ageing in skeletal muscle. This data may provide the initial evidence for several targets for potential future therapeutic interventions against sarcopenia.

Safe and Orally Bioavailable Inhibitor of Serine Palmitoyltransferase Improves Age–Related Sarcopenia

The accumulation of ceramides and related metabolites has emerged as a pivotal mechanism contributing to the onset of age-related diseases. However, small molecule inhibitors targeting the ceramide *de novo* synthesis pathway for clinical use are currently unavailable. We synthesized a safe and orally bioavailable inhibitor, termed ALT-007, targeting the rate-limiting enzyme of ceramide *de novo* synthesis, serine palmitoyltransferase (SPT). In a mouse model of age-related sarcopenia, ALT-007, administered through the diet, effectively restored muscle mass and function compromised by aging. Mechanistic studies revealed that ALT-007 enhances protein homeostasis in *Caenorhabditis elegans* and mouse models of aging and age-related diseases, such as sarcopenia and inclusion body myositis (IBM); this effect is mediated by a specific reduction in very-long chain 1-deoxy-sphingolipid species, which accumulate in both muscle and brain tissues of aged mice and in muscle cells from IBM patients. These findings unveil a promising therapeutic avenue for developing safe ceramide inhibitors to address age-related neuromuscular diseases.

Exposure to high-temperature and high-humidity environments associated with cardiovascular mortality

Aging populations are susceptible to climate change due to physiological factors and comorbidities. Most relevant studies reported the effect of temperature on cardiovascular disease (CVD)-related mortality in aging populations. However, the combined effects of temperature and humidity on CVD-related mortality remain unclear. Here we used the Global Burden of Disease (GBD) database to analyze CVD burden and its impact on the incidence of CVD in individuals exposed to high-temperature and high-humidity (HTH) environments. The prospective China Health and Retirement Longitudinal Study (CHARLS) cohort was used to further analyze the relationship between exposure to HTH environments and CVD mortality in middle-aged and elderly individuals. We found significant positive correlations between the estimated annual percentage change of CVD and age-standardized rate, wet bulb globe temperature, and Humidex worldwide. In the CHARLS, a higher CVD mortality rate was significantly associated with exposure to HTH environments ($P < 0.01$). Long-term HTH environment exposure increased the risk of an abnormal low-density lipoprotein cholesterol (LDL-C) level (hazard ratio [HR], 1.30-2.44) and abnormal total cholesterol (TC) level (HR, 1.21-2.13), but the impact on high-density lipoprotein cholesterol (HDL-C) level was unclear. The mortality risks of long-term exposure to HTH environments were increased for middle-aged and elderly individuals with abnormal LDL-C (HR = 0.84-3.57) and TC (HR = 0.78-2.41) levels. These findings suggest that exacerbated dyslipidemia caused by long-term HTH environment exposure may be a key risk factor for CVD-related mortality in middle-aged and elderly individuals and suggest research directions into the effects of HTH environments on human health.

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Distinct causes of three phenotypic hallmarks of hematopoietic aging

Hematopoietic aging is characterized by chronic inflammation associated with myeloid bias, HSC accumulation, and functional HSC impairment. Yet it remains unclear how inflammation promotes these aging phenotypes. NFκB both responds to and directs inflammation, and we present an experimental model of elevated NFκB activity ("IκB$^{-/-}$") to dissect its role in hematopoietic aging phenotypes. We found that while elevated NFκB activity is not sufficient for HSC accumulation, HSC-autonomous NFκB activity impairs their functionality, leading to reduced bone marrow reconstitution. In contrast, myeloid bias is driven by the IκB^{-} proinflammatory bone marrow milieu as observed functionally, epigenomically, and transcriptomically. A new scRNA-seq HSPC labeling framework enabled comparisons with aged murine and human HSC datasets, documenting an association between HSC-intrinsic NFκB activity and quiescence, but not myeloid bias. These findings delineate separate regulatory mechanisms that underlie the three hallmarks of hematopoietic aging, suggesting that they are specifically and independently therapeutically targetable.

Amyloid-β and tau deposition in traumatic brain injury: a study of Vietnam War veterans

Traumatic brain injury is widely viewed as a risk factor for dementia, but the biological mechanisms underlying this association are still unclear. In previous studies, traumatic brain injury has been associated with the hallmark pathologies of Alzheimer's disease, i.e. amyloid-β plaques and neurofibrillary tangles comprised of hyperphosphorylated tau. Depending on the type and location of trauma, traumatic brain injury can induce spatially heterogeneous brain lesions that may pre-dispose for the development of Alzheimer's disease pathology in aging. Therefore, we hypothesized that a history of traumatic brain injury may be related to spatially heterogeneous amyloid-β and tau pathology patterns that deviate from the stereotypical temporo-parietal patterns in Alzheimer's disease. To test this, we included 103 Vietnam War veterans of whom 65 had experienced traumatic brain injury (n = 40, 38.8% mild; n = 25, 24.3% moderate/severe). Most individuals had a history of 1 (n = 35, 53.8%) or 2 (n = 15, 23.1%) traumatic brain injury events. We included the group without a history of traumatic brain injury (n = 38, 36.9%) as controls. The majority was cognitively normal (n = 80, 77.7%), while a subset had mild cognitive impairment (n = 23, 22.3%). All participants underwent [^{18}F]florbetapir/Amyvid amyloid-β PET and [^{18}F]flortaucipir/Tauvid tau-PET 39.63 ± 18.39 years after their last traumatic brain injury event. We found no differences in global amyloid-β and tau-PET levels between groups, suggesting that a history of traumatic brain injury does not pre-dispose to accumulate amyloid-β or tau pathology in general. However, we found that traumatic brain injury was associated with altered spatial patterns of amyloid-β and tau, with relatively greater deposition in fronto-parietal brain regions. These regions are prone to damage in traumatic brain injury, while they are typically only affected in later stages of Alzheimer's disease. Moreover, in our traumatic brain injury groups, the association between amyloid-β and tau was reduced in Alzheimer-typical temporal regions but increased in frontal regions that are commonly associated with traumatic brain injury. Altogether, while acknowledging the relatively small sample size and generally low levels of Alzheimer's disease pathology in this sample, our findings suggest that traumatic brain injury induces spatial patterns of amyloid-β and tau that differ from patterns observed in typical Alzheimer's disease. Furthermore, traumatic brain injury may be associated with a de-coupling of amyloid-β and tau in regions vulnerable in Alzheimer's disease. These findings indicate that focal brain damage in early/mid-life may change neurodegenerative trajectories in late-life.

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SNP rs6543176 is associated with extreme human longevity but increased risk for cancer

Using whole-genome sequencing (WGS) might offer insights into rare genetic variants associated with healthy aging and extreme longevity (EL), potentially pointing to useful therapeutic targets. In this study, we conducted a genome-wide association study using WGS data from the Long Life Family Study and identified a novel longevity-associated variant rs6543176 in the SLC9A2 gene. This SNP also showed a significant association with reduced hypertension risk and an increased, though not statistically significant, cancer risk. The association with cancer risk was replicated in the UK Biobank and FinnGen. Metabolomic analyses linked the rs6543176 longevity allele to higher serine levels, potentially associated with delayed mortality. Our findings warrant further investigation of SLC9A2's role in both longevity and cancer susceptibility, and they highlight the need for careful evaluation in developing anti-aging therapies based on EL-associated alleles.

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IL-23R is a senescence-linked circulating and tissue biomarker of aging

Cellular senescence is an aging mechanism characterized by cell cycle arrest and a senescence-associated secretory phenotype (SASP). Preclinical studies demonstrate that senolytic drugs, which target survival pathways in senescent cells, can counteract age-associated conditions that span several organs. The comparative efficacy of distinct senolytic drugs for modifying aging and senescence biomarkers in vivo has not been demonstrated. Here, we established aging- and senescence-related plasma proteins and tissue transcripts that changed in old versus young female and male mice. We investigated responsivity to acute treatment with venetoclax, navitoclax, fisetin or luteolin versus transgenic senescent cell clearance in aged *p16-InkAttac* mice. We discovered that age-dependent changes in plasma proteins, including IL-23R, CCL5 and CA13, were reversed by senotherapeutics, which corresponded to expression differences in tissues, particularly in the kidney. In plasma from humans across the lifespan, IL-23R increased with age. Our results reveal circulating factors as candidate mediators of senescence-associated interorgan signal transduction and translationally impactful biomarkers of systemic senescent cell burden.

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TPR is required for cytoplasmic chromatin fragment formation during senescence

During oncogene-induced senescence there are striking changes in the organisation of heterochromatin in the nucleus. This is accompanied by activation of a pro-inflammatory gene expression programme – the senescence-associated secretory phenotype (SASP) – driven by transcription factors such as NF-κB. The relationship between heterochromatin re-organisation and the SASP has been unclear. Here, we show that TPR, a protein of the nuclear pore complex basket required for heterochromatin re-organisation during senescence, is also required for the very early activation of NF-κB signalling during the stress-response phase of oncogene-induced senescence. This is prior to activation of the SASP and occurs without affecting NF-κB nuclear import. We show that TPR is required for the activation of innate immune signalling at these early stages of senescence and we link this to the formation of heterochromatin-enriched cytoplasmic chromatin fragments thought to bleb off from the nuclear periphery. We show that HMGA1 is also required for cytoplasmic chromatin fragment formation. Together these data suggest that re-organisation of heterochromatin is involved in altered structural integrity of the nuclear periphery during senescence, and that this can lead to activation of cytoplasmic nucleic acid sensing, NF-κB signalling, and activation of the SASP.

Generation of a selective senolytic platform using a micelle-encapsulated Sudan Black B conjugated analog

The emerging field of senolytics is centered on eliminating senescent cells to block their contribution to the progression of age-related diseases, including cancer, and to facilitate healthy aging. Enhancing the selectivity of senolytic treatments toward senescent cells stands to reduce the adverse effects associated with existing senolytic interventions. Taking advantage of lipofuscin accumulation in senescent cells, we describe here the development of a highly efficient senolytic platform consisting of a lipofuscin-binding domain scaffold, which can be conjugated with a senolytic drug via an ester bond. As a proof of concept, we present the generation of GL392, a senolytic compound that carries a dasatinib senolytic moiety. Encapsulation of the GL392 compound in a micelle nanocarrier (termed mGL392) allows for both in vitro and in vivo (in mice) selective elimination of senescent cells via targeted release of the senolytic agent with minimal systemic toxicity. Our findings suggest that this platform could be used to enhance targeting of senotherapeutics toward senescent cells.

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Cellular Senescence Genes as Cutting-Edge Signatures for Abdominal Aortic Aneurysm Diagnosis: Potential for Innovative Therapeutic Interventions

Abdominal aortic aneurysm (AAA) is the most prevalent dilated arterial aneurysm that poses a significant threat to older adults, but the molecular mechanisms linking senescence to AAA progression remain poorly understood. This study aims to identify cellular senescence-related genes (SRGs) implicated in AAA development and assess their potential as therapeutic targets. Four hundred and twenty-nine differentially expressed genes (DEGs) were identified from the GSE57691 training set, and 867 SRGs were obtained. Through the intersection of DEGs with SRGs, 19 differentially expressed senescence-related genes (DESRGs) were uncovered. Functional enrichment analysis was performed to explore their biological roles in AAA. To identify hub genes, we applied machine learning algorithms, including LASSO, SVM-RFE and random forest. These hub genes were then validated in two independent datasets. In the initial validation cohort, significant differences in the expression levels of BTG2, ETS1, ID1 and ITPR3 were observed between the AAA and control groups. Receiver operating characteristic (ROC) analysis demonstrated a robust diagnostic performance. Further validation across different AAA stages (small, large and ruptured AAA) identified ETS1 and ITPR3 as potential diagnostic genes. Subsequently, the diagnostic relevance of ETS1 and ITPR3 was further validated in human serum samples and mouse models of AAA. In addition, single-cell RNA sequencing suggests that senescent endothelial cells play a pivotal role in AAA progression, we further confirmed the correlation between ETS1 and ITPR3 and senescent endothelial cells by WB, IF and RT-qPCR. In conclusion, our study reveals the pivotal role of cellular senescence in AAA progression and identifies ETS1 and ITPR3 as promising diagnostic biomarkers.

Repetitive injury induces phenotypes associated with Alzheimer's disease by reactivating HSV-1 in a human brain tissue model

Infection with herpes simplex virus type 1 (HSV-1) in the brains of *APOE4* carriers increases the risk of Alzheimer's disease (AD). We previously found that latent HSV-1 in a three-dimensional in vitro model of *APOE4*-heterozygous human brain tissue was reactivated in response to neuroinflammation caused by exposure to other pathogens. Because traumatic brain injury also causes neuroinflammation, we surmised that brain injury might similarly reactivate latent HSV-1. Here, we examined the effects of one or more controlled blows to our human brain model in the absence or presence of latent HSV-1 infection. After repeated, mild controlled blows, latently infected tissues showed reactivation of HSV-1; the production and accumulation of β amyloid and phosphorylated tau (which promotes synaptic dysfunction and neurodegeneration); and activated gliosis, which is associated with destructive neuroinflammation. These effects are collectively associated with AD, dementia, and chronic traumatic encephalopathy (CTE) and were increased with additional injury but were absent in mock-infected tissue. Blocking the cytokine IL-1β prevented the induction of amyloid and gliosis in latently infected monolayer cultures after scratch wounding. We thus propose that after repeated mechanical injuries to the brain, such as from direct blows to the head or jarring motions of the head, the resulting reactivation of HSV-1 in the brain may contribute to the development of AD and related diseases in some individuals.

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Boosting neuronal activity-driven mitochondrial DNA transcription improves cognition in aged mice

We demonstrate that neuronal and synaptic activity enhances mtDNA expression in excitatory neurons, a process mediated by activity-dependent mitochondrial calcium influx ($[Ca^{2+}]_{mito}$) and transcriptional control mechanisms involving mitochondrial Ca^{2+}-calmodulin–dependent protein kinase II ($CaMKII_{mito}$) and Ca^{2+}/cAMP response element–binding protein ($CREB_{mito}$). Specifically, neuronal activation induces the phosphorylation of the mitochondrial calcium uniporter (MCU) through $CaMKII_{mito}$ in an activity-dependent manner, thereby feedforward-regulating $[Ca^{2+}]_{mito}$. In turn, this activity-dependent process phosphorylates the transcription factor (TF) $CREB_{mito}$ to control mtDNA transcription and expression. Thus, E-TC_{mito} repurposes molecules traditionally associated with excitation-transcription coupling in the nucleus (E-TC_{nuc}) to regulate mitochondrial DNA transcription, which can be specifically recruited in dendritic areas closely linked to synaptic activation. In both in vitro and in vivo models, blocking E-TC_{mito} impaired activity-driven mtDNA expression and profoundly disrupted neuronal energy reserves, reducing the capacity to meet synaptic demands. This regulatory mechanism provides crucial feedback control to maintain synaptic resilience against activity challenges and plays an integral role in memory processes. Aged mice exhibited diminished activity-dependent mitochondrial calcium signaling and mtDNA expression, suggesting an age-related decline in E-TC_{mito}. Notably, expressing a constitutively active form of $CREB_{mito}$ in aged mice restored activity-dependent mtDNA expression, increased neuronal energy reserves, and enhanced memory performance, suggesting a potential strategy to mitigate age-related cognitive decline.

Cognitive interventions for healthy older adults: A systematic meta-review

Objectives: With increasing global life expectancy, cognitive interventions hold promise in mitigating cognitive decline and fostering healthy aging. Despite the demand for evidence-based interventions, there have been few attempts to summarize existing evidence. This study aims to assess the effectiveness and feasibility of unimodal and multimodal cognitive interventions for cognitively healthy older adults.

Method: Systematic meta-review, selecting articles from four databases: PubMed, Web of Science, Embase, and Cochrane Library. Quality assessment carried out with AMSTAR2. Findings were summarized and discussed narratively.

Results: Thirty-nine articles were included, with 21 meta-analyses and 18 qualitative systematic reviews. The total number of reviews was 38 for cognitive training, 4 for cognitive stimulation, and 1 for multicomponent interventions. Most reviews had low or critically low quality.

Conclusions: The prevailing evidence supports cognitive training. Continued research into cognitive stimulation and multicomponent protocols is encouraged. Longer follow-ups are important for identifying combined and clinically significant results. Rigorous risk of bias and quality assessment is necessary to enhance the evidence base.

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Deep learning reveals diverging effects of altitude on aging

Aging is influenced by a complex interplay of multifarious factors, including an individual's genetics, environment, and lifestyle. Notably, high altitude may impact aging and age-related diseases through exposures such as hypoxia and ultraviolet (UV) radiation. To investigate this, we mined risk exposure data (summary exposure value), disease burden data (disability-adjusted life years (DALYs)), and death rates and life expectancy from the Global Health Data Exchange (GHDx) and National Data Management Center for Health of Ethiopia for each subnational region of Ethiopia, a country with considerable differences in the living altitude. We conducted a cross-sectional clinical trial involving 227 highland and 202 lowland dwellers from the Tigray region in Northern Ethiopia to gain a general insight into the biological aging at high altitudes. Notably, we observed significantly lower risk exposure rates and a reduced disease burden as well as increased life expectancy by lower mortality rates in higher-altitude regions of Ethiopia. When assessing biological aging using facial photographs, we found a faster rate of aging with increasing elevation, likely due to greater UV exposure. Conversely, analysis of nuclear morphologies of peripheral blood mononuclear cells (PBMCs) in blood smears with five different senescence predictors revealed a significant decrease in DNA damage-induced senescence in both monocytes and lymphocytes with increasing elevation. Overall, our findings suggest that disease and DNA damage-induced senescence decreases with altitude in agreement with the idea that oxidative stress may drive aging.

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PREPRINT

Cigarette smoke and biological age induce degenerative heterogeneity in retinal pigment epithelium

Environmental exposure such as cigarette smoke induces epigenetic changes that can induce degenerative heterogeneity and accelerate aging. In early age-related macular degeneration (AMD), the leading worldwide cause of blindness among the elderly, retinal pigment epithelial (RPE) cell heterogeneity is a key change. Since smoking is the strongest environmental risk factor for AMD, we hypothesized that cigarette smoke induces degenerative RPE heterogeneity through epigenetic changes that are distinct from aging, and that with aging, the RPE becomes vulnerable to cigarette smoke insult. We administered cigarette smoke condensate (CSC) intravitreally to young and aged mice and performed snRNA-seq and snATAC-seq on the RPE/choroid. This analysis identified separate cell clusters corresponding to healthy and abnormal, dedifferentiated RPE in both aged vehicle-treated and young CSC-treated mice. The dedifferentiated RPE were characterized by a global decrease in chromatin accessibility and decreased expression of genes in functional categories that were linked to hallmarks of aging. Notably, young, dedifferentiated RPE also exhibited a compensatory upregulation of hallmarks of aging-related genes, specifically those related to mitochondrial function and proteostasis. In contrast, aged dedifferentiated RPE did not express these compensatory changes, and did not survive CSC treatment, as experimentally verified with TUNEL labeling. These changes are relevant to early AMD because we identified through scRNA-seq, similar dedifferentiated and healthy macular RPE clusters in a donor who smoked and another with early AMD, but not from a nonsmoker. Degenerative cellular heterogeneity can include an abnormal cluster that jeopardizes cell survival and may represent an additional hallmark of ocular aging.

A longevity-specific bank of induced pluripotent stem cells from centenarians and their offspring

Centenarians provide a unique lens through which to study longevity, healthy aging, and resiliency. Moreover, models of *human* aging and resilience to disease that allow for the testing of potential interventions are virtually non-existent. We obtained and characterized over 96 centenarian and offspring peripheral blood samples including those connected to functional independence data highlighting resistance to disability and cognitive impairment. Targeted methylation arrays were used in molecular aging clocks to compare and contrast differences between biological and chronological age in these specialized subjects. Isolated peripheral blood mononuclear cells (PBMCs) from 20 of these subjects were then successfully reprogrammed into high-quality induced pluripotent stem cell (iPSC) lines which were functionally characterized for pluripotency, genomic stability, and the ability to undergo directed differentiation. The result of this work is a one-of-a-kind resource for studies of human longevity and resilience that can fuel the discovery and validation of novel therapeutics for aging-related disease.

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PREPRINT

Feasibility of intravenous injections of pig plasma extracellular particles into rats — an acute study

Nicolás Cherñavsky, Stepheny C. de Campos Zani, Marcelo A. Mori, Nina T. Zanvettor

Background Extracellular particles (EPs), especially small extracellular vesicles (EVs), extracted from young animals are increasingly being studied in animal models as agents for regeneration and rejuvenation, with studies using EPs from one species injected into another showing no immune reaction. In this study, we aimed to investigate if the injection of Pig Plasma Extracellular Particles (PPEPs) into rats would produce an acute immune or toxic reaction.

Methods Blood from a young pig was collected, PPEPs were isolated by size exclusion chromatography and injected into young male Sprague-Dawley rats, while the control group received a sterile saline injection. After 9 days, the animals were euthanized and their organs were histologically analyzed for signs of cellular damage or immune infiltration.

Results The treated rats showed no signs of acute immunological reaction, behaving normally immediately after the injections and during the 9 days since the first injection. Throughout the trial period, the animals continued gaining weight normally and the histological analysis of their liver, kidney and spleen showed no signs of acute toxicity.

Conclusions PPEPs from young animals do not cause an acute immune or toxic response when injected intravenously into young male Sprague-Dawley rats.

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ECM Modifications Driven by Age and Metabolic Stress Directly Promote the Vascular Smooth Muscle Cell Osteogenic Processes

Background: The ECM (extracellular matrix) provides the microenvironmental niche sensed by resident vascular smooth muscle cells (VSMCs). Aging and disease are associated with dramatic changes in ECM composition and properties; however, their impact on the VSMC phenotype remains poorly studied.

Methods: Here, we describe a novel in vitro model system that utilizes endogenous ECM to study how modifications associated with age and metabolic disease impact the VSMC phenotype. ECM was synthesized using primary human VSMCs and modified during culture or after decellularization. Integrity, stiffness, and composition of the ECM was measured using superresolution microscopy, atomic force microscopy, and proteomics, respectively. VSMCs reseeded onto the modified ECM were analyzed for viability and osteogenic differentiation.

Results: ECMs produced in response to mineral stress showed extracellular vesicle-mediated hydroxyapatite deposition and sequential changes in collagen composition and ECM properties. VSMCs seeded onto the calcified ECM exhibited increased extracellular vesicle release and Runx2 (Runt-related transcription factor 2)-mediated osteogenic gene expression due to the uptake of hydroxyapatite, which led to increased reactive oxygen species and the induction of DNA damage signaling. VSMCs seeded onto the nonmineralized, senescent ECM also exhibited increased Runx2-mediated osteogenic gene expression and accelerated calcification. In contrast, glycated ECM specifically induced increased ALP (alkaline phosphatase) activity, and this was dependent on RAGE (receptor for advanced glycation end products) signaling with both ALP and RAGE receptor inhibition attenuating calcification.

Conclusions: ECM modifications associated with aging and metabolic disease can directly induce osteogenic differentiation of VSMCs via distinct mechanisms and without the need for additional stimuli. This highlights the importance of the ECM microenvironment as a key driver of phenotypic modulation acting to accelerate age-associated vascular pathologies and provides a novel model system to study the mechanisms of calcification.

Temporally and Spatially Controlled Age-Related Prostate Cancer Model in Mice

Sen Liu [1], Keyi Shen [1], Zixuan Li [1], Seleste Rivero [1], Qiuyang Zhang [1 2 3]

The initiation and progression of prostate cancer (PCa) are associated with aging. In the history of age-related PCa research, mice have become a more popular animal model option than any other species due to their short lifespan and rapid reproduction. However, PCa in mice is usually induced at a relatively young age, while it spontaneously develops in humans at an older age. Thus, it is essential to develop a method by which the PCa initiation and progression timeline can be strictly controlled to mimic human physiological conditions. One milestone in this field was the identification of the prostate-specific transcription factor, Probasin (Pb), which allowed for the prostate-specific expression of genes knocked into the mice's genome. Another milestone is the establishment of the preclinical mouse model with *Pten* conditionally knocked out in the prostate tissue, which closely mimics the formation and growth of human PCa. Hereby, we present the prostate-specific temporally and spatially controlled *Pten* knockout PCa mouse model that can be induced using an adenovirus-based Cre-LoxP system. The Cre recombinase (Cre) is inserted into an adenovirus vector. Unlike Pb-Cre knock-in models (which are spatially but not temporally controlled), the expression of Cre is activated to knock out *Pten* from the mice's prostate epithelial cells once injected. The viral delivery procedures strictly control the location and time of *Pten* knockout. This novel approach provides a powerful age-related murine model for PCa, emphasizing the effect of aging on prostate carcinogenesis. Key features • In vivo delivery of Cre recombinase adenovirus (Ad-Cre-Luc) in *Pten* LoxP/LoxP (L/L) mice. • Generation of Cre-expressing Ad-Cre-Luc-mediated ablation of *Pten* in anterior prostate epithelial cells of adult *Pten* L/L mice at different ages. • The Ad-Cre-Luc-mediated ablation of *Pten* leads to hyperplasia that progresses through prostatic intraepithelial neoplasia (PIN) to adenocarcinoma. • PIN refers to the non-cancerous growth of epithelial cells in the prostate tissue-not cancer but a precursor of prostate cancer [1].

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PREPRINT

Tissue-specific modulation of NADH consumption as an anti-aging intervention in Drosophila

Aging is characterized by extensive metabolic dysregulation. Redox coenzyme nicotinamide adenine dinucleotide (NAD) can exist in oxidized (NAD^+) or reduced (NADH) states, which together form a key NADH/NAD^+ redox pair. Total levels of NAD decline with age in a tissue-specific manner, thereby playing a significant role in the aging process. Supplementation with NAD precursors boosts total cellular NAD levels and provides some therapeutic benefits in human clinical trials. However, supplementation studies cannot determine tissue-specific effects of an altered NADH/NAD^+ ratio. Here, we created transgenic *Drosophila* expressing a genetically encoded xenotopic tool *Lb*NOX to directly manipulate the cellular NADH/NAD^+ ratio. We found that *Lb*NOX expression in *Drosophila* impacts both NAD(H) and NADP(H) metabolites in a sex-specific manner. *Lb*NOX rescues neuronal cell death induced by the expression of mutated alpha-B crystallin in the *Drosophila* eye, a widely used system to study reductive stress. Utilizing *Lb*NOX, we demonstrate that targeting redox NAD metabolism in different tissues may have drastically different outcomes, as the expression of *Lb*NOX solely in the muscle is much more effective for rescuing paraquat-induced oxidative stress compared to whole-body expression. Excitingly, we demonstrate that perturbing NAD(P) metabolism in non-neuronal tissues is sufficient to rejuvenate sleep profiles in aged flies to a youthful state. In summary, we used xenotopic tool *Lb*NOX to identify tissues and metabolic processes which benefited the most from the modulation of the NAD metabolism thereby highlighting important aspects of rebalancing the NAD and NADP pools, all of which can be translated into novel designs of NAD-related human clinical trials.

Association between ultra-processed food intake and biological ageing in US adults: findings from National Health and Nutrition Examination Survey (NHANES) 2003–2010

Methods

This cross-sectional study assessed 16 055 participants aged 20–79 years (51% women, 46 ± 0.3 years) from the National Health and Nutrition Examination Survey (NHANES) 2003–2010. Dietary UPF intake was assessed using the Nova system. Values were expressed as % of total energy intake and were denominated as a continuous variable and in quintiles. Diet quality was assessed with the American Heart Association 2020 and the Healthy Eating Index 2015. Biological ageing was assessed **using the PhenoAge algorithm**.

Results

For each 10% of energy intake accounted for by UPF, participants were 0.21 (95%CI 0.16–0.26) years biologically older in terms of PhenoAge. As compared to participants in the lowest UPF quintile (≤39%), those in the highest UPF quintile (68–100%) were 0.86 (95% CI 0.55, 1.16) years older (P-for-trend across quintiles ≤0.001). Adherence to a healthy diet moderately attenuated the relationship between UPF and PhenoAge (adjusted β = 0.14 per 10% increment of UPF).

Conclusions

Adults with higher UPF tended to be biologically older. This association is partly independent of diet quality, suggesting that food processing may contribute to biological ageing acceleration. Our findings point to a compelling reason to target UPF consumption to promote healthier ageing.

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Conference abstract

LIFE EXTENSION VIA GENETIC/DRUG INTERVENTIONS OCCURS BY DELAYING THE ONSET OF AGING, NOT BY SLOWING THE RATE OF AGING

Patrick Phillips [1], Christine Sedore [2], Grace Jackson [3], Gordon Lithgow [4], Monica Driscoll [5]

Ever since the discovery more than 30 years ago of mutations capable dramatically increasing lifespan, there has been an increasing push to find genetic pathways and chemical interventions that ameliorate the effects of aging and increase healthspan and longevity. But aging is not merely "getting old," it is an accelerating rate of the decline in function and an increase in the rate of mortality with chronological age. Here, we present a new framework for understanding longevity-extending interventions by dividing the survivorship into two major parts—the onset of aging and the period of accelerated aging—and use a uniform analytical approach to derive these quantities for each of the major mortality models. We apply this new framework to a set of studies with sufficient size to estimate mortality rate, finding that for four genetic and three chemical interventions in C. elegans and five genetic and eleven chemical interventions in mice, all treatments that lead to an increase in overall lifespan do so by delaying the onset of aging and none decrease the rate of aging late in life. These effects are readily visualized using a relative hazard and relative lifespan approach. Thus, while there is great interest identify compounds and other approaches to "treat" aging, evidence to date suggests that these interventions do not actually affect aging in the formal sense. These results have important implications for the design and analysis of aging studies, as well as for the field of geroscience as a whole.

Conference abstract

NEW TOOL ENHANCES DETECTION OF LIFE-EXTENDING INTERVENTIONS BY DELINEATING THEIR TEMPORAL EFFICACY

Nisi Jiang [1], Qianqian Liu [2], Catherine Cheng [3], Randy Strong [4], Jonathan Gelfond [5], James Nelson [6]

Drug discovery of anti-aging interventions relies on survival data, which is time-consuming and costly to generate, yet the analysis of such data often fails to capitalize on its full potential. The predominant method for assessing intervention effects on lifespan, the log-rank test, lacks the power to identify when and for how long an intervention is effective. Moreover, it has decreased sensitivity for interventions that are only effective during part of the life course. Statistical tools are needed to address these limitations. They should be capable of identifying when, for how long, and to what extent an intervention reduces (or increases) mortality risk. Here we introduce a Temporal Efficacy Profiler (TEP), which meets these needs, and apply it to survival data from 42 compounds tested in the NIA Interventions Testing Program (ITP) using UM-HET3 mice. Compared to the log-rank test, this tool identified over twice as many compounds that increased (or decreased) survival, largely because of its sensitivity to variable efficacy of the interventions across the life course. Sex differences were prevalent. The TEP revealed agents that either reduced (22 compounds) or increased (15 compounds) mortality hazards, with some (2 compounds) showing dual effects depending on sex. Notably, the efficacy of these interventions varied significantly in both duration and magnitude. Moreover, the TEP uncovered adverse effects that were missed by the log-rank test. Of note, only 8 compounds significantly reduced mortality hazards beyond the 90th percentile of mortality, a period when the burden of senescence is highest.

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Conference abstract

BLOOD MULTIOMIC PROFILES REFLECT SYSTEM STATES OF ORGANS IN MICE

Kengo Watanabe [1], Lance Pflieger [2], Max Robinson [3], Jodi Lapidus [4], Richard Miller [5], Oliver Fiehn [6], Robert Moritz [7], Noa Rappaport [8]

The rate of aging can vary among organs, as evidenced by organ-specific biological age models. Such models are typically constructed based on the blood biomarkers or phenotypes that are known to be specific to a particular organ. However, this approach potentially limits the models to reflecting only a narrow scope of organ system states. Herein, we report the potential of blood omics data to reflect alterations in organ systems, using the NIA Longevity Consortium mouse prolongenvity proteomics and metabolomics data which were derived from kidney, liver, gastrocnemius muscle, and plasma samples from each mouse. While correlation analysis mainly identified the correlations of matched analytes between organs and blood, machine learning models to predict the organ analyte abundance or system state from the plasma analytes revealed the differences between sexes or prolongevity interventions. Our findings suggest the power of blood omics for identifying and characterizing diverse system states of organs involved in aging and longevity.

Conference abstract

A PROTEOMICS-BASED MEASURE OF ACCELERATING AGING IS CORRELATED WITH THE BRAIN AGE GAP IN THE ARIC STUDY

Ramon Casanova [1], Keenan Walker [2], Lingyi Lu [3], Stephen Kritchevsky [4], Timothy Hughes [5], Lynne Wagenknecht [6]

Proteomics clocks can be used to estimate chronologic age or predict age-related outcomes (e.g., GrimAge or AgeAccelGrim and mortality). Analogous to AgeAccelGrim, we developed a proteomic predictor in the Atherosclerosis Risk in Communities (ARIC) Study, and present correlations between this measure and an MRI-derived measure of advanced brain age (brain age gap) and other clinical parameters. We used data from 1447 ARIC participants with both brain MRIs and proteins levels available. The data was partitioned into training and testing datasets (75%-25%). We fitted a Cox regression elastic net model to predict all-cause mortality based on all proteins available in the SOMAscan aptamer panel (N = 4877), age and sex. The linear combination of variables was transformed to match mean age and variance of the training dataset. Finally, the age was regressed out to produce the proteomic measure. The testing dataset was used to estimate Spearman correlations. In total 33 proteins were selected by the model including R-sponding-4, GDF-15, ANGPT2 and PCYOX1L with larger (positives) coefficients while F7, SET and CNDP1 were the ones with smaller (negative) coefficients. The proteomic age measure was correlated with the brain age gap (0.26 $p < 0.001$), hypertension (0.25 $p < 0.001$), diabetes (0.18 $p < 0.001$), gait speed (0.24 $p < 0.001$), total cholesterol (0.25 $p < 0.001$) but not correlated with fasting glucose, grip strength or MRI-derived temporal meta-ROI. These results here link brain and body indices of accelerated aging independently of chronological age. Further investigation of the interrelationships between brain and proteomics aging measures is warranted.

C. elegans aging research

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PREPRINT

Inhibition of cytosolic translation mitigates mitochondrial dysfunction in *C. elegans*

The mitochondrial unfolded protein response (UPR^{mt}) is regulated by the bZIP protein ATFS-1 which promotes mitochondrial protein homeostasis (proteostasis) and mitochondrial biogenesis in *Caenorhabditis elegans*. Upon mitochondrial perturbation, the ATFS-1-dependent transcriptional program promotes gene expression, leading to mitochondrial recovery. Conversely, *atfs-1*-deletion worms harbor dysfunctional mitochondria, are developmentally impaired, and short-lived. However, *atfs-1*-deletion worms develop to adults suggesting the presence of other signaling pathways that promote mitochondrial function and biogenesis in the absence of *atfs-1*. We hypothesized that additional transcription factors regulate, or promote, mitochondrial function in the absence of *atfs-1*. Here, we screened for transcription factors that could reduce the decline in mitochondrial function in the atfs-1 mutants when inhibited. Here, we demonstrate that inhibition of the nuclear hormone receptor NHR-180 re-establishes a functional mitochondrial network in *atfs-1(null)* worms, increases mtDNA content, and improves the developmental rate of wildtype worms. NHR-180 increases transcription of genes required for cytosolic protein synthesis in response to mitochondrial perturbation. Inhibition of the S6 kinase homolog, *rsks-1*, in *atfs-1(null)* worms leads to a recovery of the mitochondrial network and mtDNA content consistent with *nhr-180* regulating expression of protein synthesis components. Consistent with the observations in *C. elegans*, S6 kinase inhibition also increased mitochondrial biogenesis in mammalian *atf5*-knockout cells that harbor severely impaired mitochondria. Intriguingly, *nhr-180* or S6 kinase inhibition also rescues mitochondrial dysfunction caused by mutations in multiple genes required for oxidative phosphorylation. Combined, these studies suggest that increased protein synthesis contributes to the mitochondrial dysfunction caused by perturbations in OXPHOS gene expression and suggest a relatively straightforward approach to reducing the impact of mitochondrial dysfunction.

REVIEWS/COMMENTS/ METHODS/EDITORIALS

Balancing the promise and risks of geroscience interventions

Alan A Cohen [1], John R Beard [2], Luigi Ferrucci [3], Tamàs Fülöp [4 5], Vadim N Gladyshev [6], Mahdi Moqri [6], Marcel G M Olde Rikkert [7], Martin Picard [8 9]

Although the emerging field of geroscience holds great promise for identifying new approaches to improve healthspan, several risks of the current framework are underappreciated. Long time horizons, challenges in identifying causality-driven surrogate biomarkers of aging, and the potential for biological trade-offs and antagonistic effects across various timescales mean it will be hard to know when such interventions have a net benefit. We propose eight strategies to mitigate these risks going forwards.

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Brown adipose tissue enhances exercise performance and healthful longevity

Brown adipose tissue (BAT), a major subtypes of adipose tissues, is known for thermogenesis and promoting healthful longevity. Our hypothesis is that BAT protects against impaired healthful longevity, i.e., obesity, diabetes, cardiovascular disorders, cancer, Alzheimer's disease, and reduced exercise tolerance. While most prior studies have shown that exercise regulates BAT activation and improves BAT density, relatively few have shown that BAT increases exercise performance. In contrast, our recent studies with the regulator of G protein signaling 14 (RGS14) knockout (KO) model of extended longevity showed that it enhances exercise performance, mediated by its more potent BAT, compared with BAT from wild type mice. For example, when the BAT from RGS14 KO mice is transplanted to WT mice, their exercise capacity is enhanced at 3 days after BAT transplantation, whereas BAT transplantation from WT to WT mice increased exercise performance, but only at 8 weeks after transplantation. The goal of this research perspective is to review the role of BAT in mediating healthful longevity, specifically exercise capacity. In view of the ability of BAT to mediate healthful longevity and enhance exercise performance, it is likely that a pharmaceutical analog of BAT will become a novel therapeutic modality.

Sarcopenia and cachexia: molecular mechanisms and therapeutic interventions

Sarcopenia is defined as a muscle-wasting syndrome that occurs with accelerated aging, while cachexia is a severe wasting syndrome associated with conditions such as cancer and immunodeficiency disorders, which cannot be fully addressed through conventional nutritional supplementation. Sarcopenia can be considered a component of cachexia, with the bidirectional interplay between adipose tissue and skeletal muscle potentially serving as a molecular mechanism for both conditions. However, the underlying mechanisms differ. Recognizing the interplay and distinctions between these disorders is essential for advancing both basic and translational research in this area, enhancing diagnostic accuracy and ultimately achieving effective therapeutic solutions for affected patients. This review discusses the muscle microenvironment's changes contributing to these conditions, recent therapeutic approaches like lifestyle modifications, small molecules, and nutritional interventions, and emerging strategies such as gene editing, stem cell therapy, and gut microbiome modulation. We also address the challenges and opportunities of multimodal interventions, aiming to provide insights into the pathogenesis and molecular mechanisms of sarcopenia and cachexia, ultimately aiding in innovative strategy development and improved treatments.

Recent advances in biomarkers for senescence: Bridging basic research to clinic

In this review, we review the current status of biomarkers for aging and possible perspectives on anti-aging or rejuvenation from the standpoint of biomarkers. Aging is observed in all cells and organs, and we focused on research into senescence in the skin, musculoskeletal system, immune system, and cardiovascular system. Commonly used biomarkers include SA-βgal, cell-cycle markers, senescence-associated secretory phenotype (SASP) factors, damage-associated molecular patterns (DAMPs), and DNA-damage-related markers. In addition, each organ or cell has its specific markers. Generally speaking, a combination of biomarkers is required to define age-related changes. When considering the translation of basic research, biomarkers that are highly sensitive, highly specific, with validation and reliability as well as being non-invasive are optimal; however, currently reported markers do not fulfill the prerequisite for biomarkers. In addition, rodent models of aging do not necessarily represent human aging, and markers in rodent or cell models are not applicable in clinical settings. The prerequisite of clinically applicable biomarkers is that they provide useful information for clinical decision-making, such as predicting disease risk, diagnosing disease, monitoring disease progression, or guiding treatment decisions. Therefore, the development of non-invasive robust, reliable, and useful biomarkers in humans is necessary to develop anti-aging therapy for humans. Geriatr Gerontol Int 2025; ••: ••-••.

Sex-specific mechanisms in vascular aging: exploring cellular and molecular pathways in the pathogenesis of age-related cardiovascular and cerebrovascular diseases

Aging remains the foremost risk factor for cardiovascular and cerebrovascular diseases, surpassing traditional factors in epidemiological significance. This review elucidates the cellular and molecular mechanisms underlying vascular aging, with an emphasis on sex differences that influence disease progression and clinical outcomes in older adults. We discuss the convergence of aging processes at the macro- and microvascular levels and their contributions to the pathogenesis of vascular diseases. Critical analysis of both preclinical and clinical studies reveals significant sex-specific variations in these mechanisms, which could be pivotal in understanding the disparity in disease morbidity and mortality between sexes. The review highlights key molecular pathways, including oxidative stress, inflammation, and autophagy, and their differential roles in the vascular aging of males and females. We argue that recognizing these sex-specific differences is crucial for developing targeted therapeutic strategies aimed at preventing and managing age-related vascular pathologies. The implications for personalized medicine and potential areas for future research are also explored, emphasizing the need for a nuanced approach to the study and treatment of vascular aging.

OTHER RESEARCH & REVIEWS

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Haematological setpoints are a stable and patient-specific deep phenotype

The complete blood count (CBC) is an important screening tool for healthy adults and a common test at periodic exams. However, results are usually interpreted relative to one-size-fits-all reference intervals[1,2], undermining the precision medicine goal to tailor care for patients on the basis of their unique characteristics[3,4]. Here we study thousands of diverse patients at an academic medical centre and show that routine CBC indices fluctuate around stable values or setpoints[5], and setpoints are patient-specific, with the typical healthy adult's nine CBC setpoints distinguishable as a group from those of 98% of other healthy adults, and setpoint differences persist for at least 20 years. Haematological setpoints reflect a deep physiologic phenotype enabling investigation of acquired and genetic determinants of haematological regulation and its variation among healthy adults. Setpoints in apparently healthy adults were associated with significant variation in clinical risk: absolute risk of some common diseases and morbidities varied by more than 2% (heart attack and stroke, diabetes, kidney disease, osteoporosis), and absolute risk of all-cause 10 year mortality varied by more than 5%. Setpoints also define patient-specific reference intervals and personalize the interpretation of subsequent test results. In retrospective analysis, setpoints improved sensitivity and specificity for evaluation of some common conditions including diabetes, kidney disease, thyroid dysfunction, iron deficiency and myeloproliferative neoplasms. This study shows CBC setpoints are sufficiently stable and patient-specific to help realize the promise of precision medicine for healthy adults.

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Burdens of type 2 diabetes and cardiovascular disease attributable to sugar-sweetened beverages in 184 countries

Laura Lara-Castor, Meghan O'Hearn, Frederick Cudhea, Victoria Miller, Peilin Shi, Jianyi Zhang, Julia R. Sharib, Sean B. Cash, Simon Barquera, Renata Micha, Dariush Mozaffarian & Global Dietary Database

The consumption of sugar-sweetened beverages (SSBs) is associated with type 2 diabetes (T2D) and cardiovascular diseases (CVD). However, an updated and comprehensive assessment of the global burden attributable to SSBs remains scarce. Here we estimated SSB-attributable T2D and CVD burdens across 184 countries in 1990 and 2020 globally, regionally and nationally, incorporating data from the Global Dietary Database, jointly stratified by age, sex, educational attainment and urbanicity. In 2020, 2.2 million (95% uncertainty interval 2.0–2.3) new T2D cases and 1.2 million (95% uncertainty interval 1.1–1.3) new CVD cases were attributable to SSBs worldwide, representing 9.8% and 3.1%, respectively, of all incident cases. Globally, proportional SSB-attributable burdens were higher among men versus women, younger versus older adults, higher- versus lower-educated adults, and adults in urban versus rural areas. By world region, the highest SSB-attributable percentage burdens were in Latin America and the Caribbean (T2D: 24.4%; CVD: 11.3%) and sub-Saharan Africa (T2D: 21.5%; CVD: 10.5%). From 1990 to 2020, the largest proportional increases in SSB-attributable incident T2D and CVD cases were in sub-Saharan Africa (+8.8% and +4.4%, respectively). Our study highlights the countries and subpopulations most affected by cardiometabolic disease associated with SSB consumption, assisting in shaping effective policies and interventions to reduce these burdens globally.

Atlas of the plasma proteome in health and disease in 53,026 adults

Yue-Ting Deng [1,9] · Jia You [1,2,3,9] · Yu He [1,9] · … · Jian-Feng Feng [2,3,8,10] · Wei Cheng [1,2,3] · Jin-Tai Yu [1]
… Show more

Large-scale proteomics studies can refine our understanding of health and disease and enable precision medicine. Here, we provide a detailed atlas of 2,920 plasma proteins linking to diseases (406 prevalent and 660 incident) and 986 health-related traits in 53,026 individuals (median follow-up: 14.8 years) from the UK Biobank, representing the most comprehensive proteome profiles to date. This atlas revealed 168,100 protein-disease associations and 554,488 protein-trait associations. Over 650 proteins were shared among at least 50 diseases, and over 1,000 showed sex and age heterogeneity. Furthermore, proteins demonstrated promising potential in disease discrimination (area under the curve [AUC] > 0.80 in 183 diseases). Finally, integrating protein quantitative trait locus data determined 474 causal proteins, providing 37 drug-repurposing opportunities and 26 promising targets with favorable safety profiles. These results provide an open-access comprehensive proteome-phenome resource (https://proteome-phenome-atlas.com/) to help elucidate the biological mechanisms of diseases and accelerate the development of disease biomarkers, prediction models, and therapeutic targets.