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Scientific News
10th of January 2026
Sven Bulterijs

Business/Conferences/ General news

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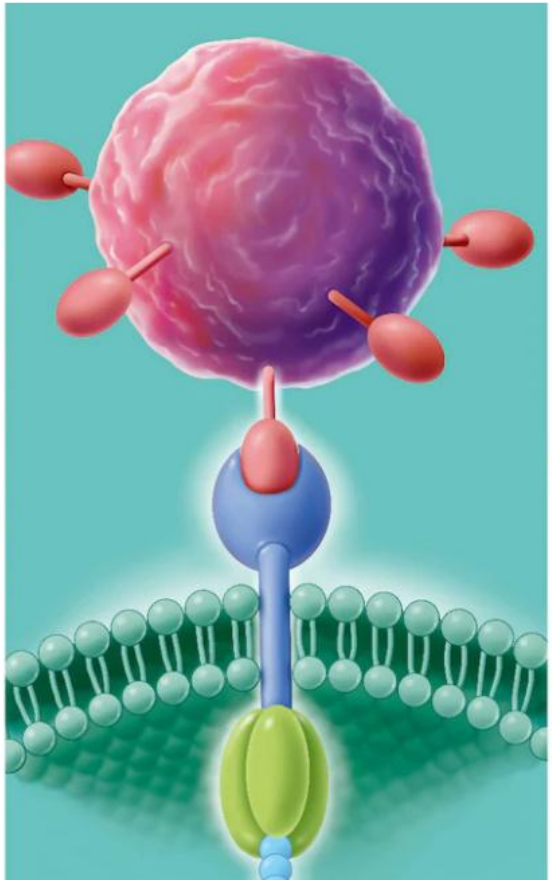
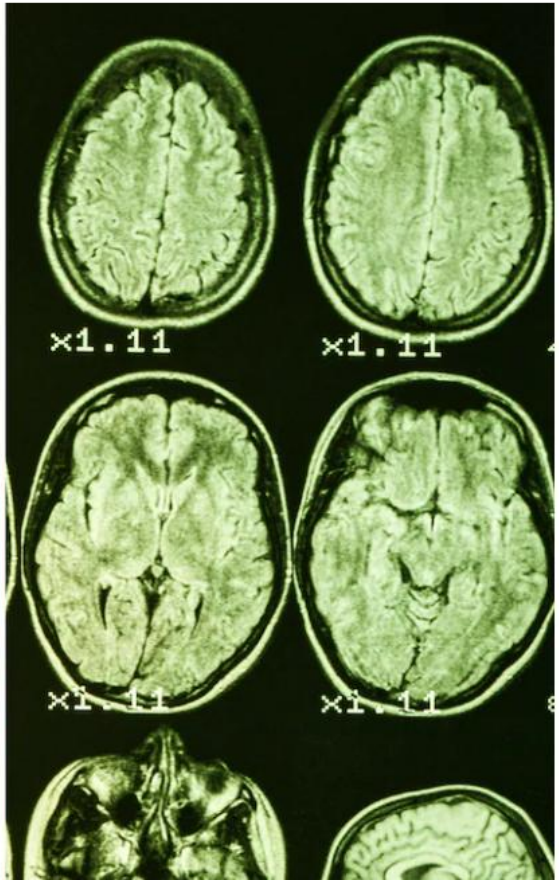
Vier hoopgevende medische doorbraken in 2025: ‘Dit is de toekomst van de geneeskunde’





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AI drug designer Insilico Medicine aims to generate nearly $300M in Hong Kong IPO

By **Conor Hale** · Dec 18, 2025 11:17am

Aging research articles

Prevalence of Alzheimer's disease pathology in the community

The prevalence of Alzheimer's disease neuropathological changes (ADNCs), the leading cause of cognitive impairment, remains uncertain. Recent blood-based biomarkers enable scalable assessment of ADNCs[1]. Here we measured phosphorylated tau at threonine 217 in 11,486 plasma samples from a Norwegian population-based cohort of individuals over 57 years of age as a surrogate marker for ADNCs. The estimated prevalence of ADNCs increased with age, from less than 8% in people 58–69.9 years of age to 65.2% in those over 90 years of age. Among participants aged 70 years or older, 10% had preclinical Alzheimer's disease, 10.4% had prodromal Alzheimer's disease and 9.8% had Alzheimer's disease dementia. Furthermore, among those 70 years of age or older, ADNCs were present in 60% of people with dementia, in 32.6% of those with mild cognitive impairment and in 23.5% of the cognitively unimpaired group. Our findings suggest a higher prevalence of Alzheimer's disease dementia in older individuals and a lower prevalence of preclinical Alzheimer's disease in younger groups than previously estimated[2].

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A multimodal sleep foundation model for disease prediction

Sleep is a fundamental biological process with broad implications for physical and mental health, yet its complex relationship with disease remains poorly understood. Polysomnography (PSG)—the gold standard for sleep analysis—captures rich physiological signals but is underutilized due to challenges in standardization, generalizability and multimodal integration. To address these challenges, we developed SleepFM, a multimodal sleep foundation model trained with a new contrastive learning approach that accommodates multiple PSG configurations. Trained on a curated dataset of over 585,000 hours of PSG recordings from approximately 65,000 participants across several cohorts, SleepFM produces latent sleep representations that capture the physiological and temporal structure of sleep and enable accurate prediction of future disease risk. From one night of sleep, SleepFM accurately predicts 130 conditions with a C-Index of at least 0.75 (Bonferroni-corrected $P < 0.01$), including all-cause mortality (C-Index, 0.84), dementia (0.85), myocardial infarction (0.81), heart failure (0.80), chronic kidney disease (0.79), stroke (0.78) and atrial fibrillation (0.78). Moreover, the model demonstrates strong transfer learning performance on a dataset from the Sleep Heart Health Study—a dataset that was excluded from pretraining—and performs competitively with specialized sleep-staging models such as U-Sleep and YASA on common sleep analysis tasks, achieving mean F_1 scores of 0.70–0.78 for sleep staging and accuracies of 0.69 and 0.87 for classifying sleep apnea severity and presence. This work shows that foundation models can learn the language of sleep from multimodal sleep recordings, enabling scalable, label-efficient analysis and disease prediction.

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Revealing the genetic architectures underlying organ-specific aging based on proteomic data

Organ-specific plasma protein signatures identified via proteomics profiling could be used to quantitatively track organ aging. However, the genetic determinants and molecular mechanisms underlying the organ-specific aging process remain poorly characterized. Here we integrated large-scale plasma proteomic and genomic data from 51,936 UK Biobank participants to uncover the genetic architectures underlying aging across 13 organs. We identified 119 genetic loci associated with organ aging, including 27 shared across multiple organs, and prioritized 554 risk genes involved in organ-relevant biological pathways, such as T cell–mediated immunity in immune aging. Causal inference analyses indicated that accelerated heart and muscle aging increase the risk of heart failure, whereas kidney aging contributes to hypertension. Moreover, smoking initiation was positively linked to the aging of the lung, intestine, kidney, and stomach. These findings establish a genetic foundation for understanding organ-specific aging and provide insights for promoting healthy longevity.

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Discrimination of normal from slow-aging mice by plasma metabolomic and proteomic features

Tests that can predict whether a drug is likely to extend mouse lifespan could speed up the search for anti-aging drugs. We have applied a machine learning algorithm, XGBoost regression, to seek sets of plasma metabolites (n = 12,000) and peptides (n = 17,000) that can discriminate control mice from mice treated with one of five anti-aging interventions (n = 278 mice). When the model is trained on any four of these five interventions, it predicts significantly higher lifespan extension in mice exposed to the intervention which was not included in the training set. Plasma peptide data sets also succeed at this task. Models trained on drug-treated normal mice also discriminate long-lived mutant mice from their respective controls, and models trained on males can discriminate drug-treated from control females. Triglycerides are over-represented among the most influential features in the regression models. Triglycerides with longer fatty acid chains tend to be higher in the slow-aging mice, while triglycerides with shorter fatty acid chains tend to decrease. Plasma metabolite patterns may help to select the most promising anti-aging drugs in mice or in humans and may give new leads into physiological and enzymatic targets relevant to the discovery of new anti-aging drugs.

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An unbiased comparison of 14 epigenetic clocks in relation to 174 incident disease outcomes

Epigenetic Clocks have been trained to predict chronological age, healthspan and lifespan. Such clocks are often analysed in relation to disease outcomes – typically using small datasets and a limited number of clocks. Here, we present a large-scale (n = 18,859), unbiased comparison of 14 widely used clocks as predictors of 174 incident disease outcomes and all-cause mortality over 10-years of follow up. Second- and third-generation clocks significantly outperform first-generation clocks, which have limited applications in disease settings. Of the 176 Bonferroni significant ($P < 0.05/174$) associations from fully-adjusted Cox regression models controlling for lifestyle and socioeconomic measures, there are 27 diseases (including primary lung cancer and diabetes) where the hazard ratio for the clock exceeds the clock's association with all-cause mortality. Furthermore, for 32 of the 176 findings, adding the clock to a null classification model with traditional risk factors significantly increases the classification accuracy by >1%. However, there is minimal evidence for interactions between the clocks and sex or smoking (ever/never) status. Second- and third-generation epigenetic clocks show promise for disease risk prediction, particularly in relation to respiratory and liver-based conditions.

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PREPRINT

Whole blood transcriptional signatures of age and survival identified in Long Life Family and Integrative Longevity Omics Studies

Although aging is a universal event, some individuals are able to achieve extreme longevity. The Long-Life Family Study (LLFS) enrolls participants from families enriched with long-lived individuals, serves as a valuable dataset for studying ageing phenotypes and identify potential intervention targets. We analyzed the association between age at blood draw and 16,284 RNAseq-based blood transcriptomic data from 2,167 LLFS participants with ages ranging from 18 to 107, replicated the results in the Integrative Longevity Omics Study (ILO) dataset of 20,884 RNAseq-based blood transcriptomic data from 419 participants, with ages ranging from 60 to 108, and further compared our findings to a published reference aging signature.

We identified 4,227 transcripts increasing and 4,044 transcripts decreasing with age, and enrichment analysis revealed age-related upregulation of inflammatory and senescence-related pathways, and downregulation of MYC and Wnt/β-catenin targets, among others. Further, a subset of transcripts showed age associations unique to the longevity-enriched cohorts (LLFS and ILO). We also identified 314 transcripts significantly associated with mortality risk and found that pro-survival gene sets included NK cell-mediated cytotoxicity and GPCR signaling. Finally, increased transcriptomic age predicted using transcriptomic clock was strongly associated with increased mortality. In summary, this study identified robust transcriptomic signatures of aging and mortality in a longevity-enriched population, highlighting key biological pathways such as immune modulation, inflammation, and senescence.

Graded Calorie Restriction Causes Graded Slowing of Epigenetic Ageing in Mice

Timothy P Moulds [1], Sharon E Mitchell [1], Xiaojing Yang [2], Wei Guo [2], Emily Chen [2], Peter D Adams [3], John R Speakman [1 4 5 6]

DNA methylation variation is associated with chronological ageing. Calorie restriction (CR) prolongs lifespan and healthspan in many species. Our hypothesis is that CR has an impact on DNA methylation patterns with increased CR leading to slower epigenetic ageing. We studied the effects of graded CR in male C57BL/6J mice on liver DNA methylation. Mice were fed ad libitum (AL) in the dark-phase or restricted by 10%, 20%, 30% or 40% from 5-months old for 19-months. Livers were collected in surviving mice at 24-months old and DNA methylation measured. Comparisons were made to 8-month-old AL fed mice. DNA methylation was significantly related to graded CR in a subset of cytosine-guanine dinucleotide (CpG) sites. In a substantially similar subset of CpG sites, DNA methylation in 24-month-old mice fed 40CR moved towards the values in 8-month-old AL fed mice, resulting in an average effective epigenetic age of about 12-months, indicative of slower epigenetic ageing. DNA methylation at several CpG sites was sensitive to glucose intolerance and circulating insulin levels, consistent with the impact of this nutrient sensing pathway on ageing. We focussed on genes where multiple CpG sites were significant for DNA methylation change with CR and found many have been implicated in age-associated liver diseases. In summary, the benefits of CR include modification of epigenetic signatures in the direction of slower ageing, consistent with the life extending effects of CR. Whether this effect is causal for the life extension under CR, and the mechanism by which it occurs remain unanswered questions.

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Not Aging but Calorie Restriction Strongly Affects Protein Oxidation in Heart and Brain Mitochondria

Aging is an inevitable consequence for all organisms. According to the mitochondrial free radical theory of aging (MFRTA), reactive oxygen species (ROS), which are predominantly generated in mitochondria, are assumed to play a key role. Calorie restriction (CR) delays aging by improving mitochondrial function; however, the molecular mechanisms underlying the effects of ROS and CR on mitochondria remain poorly understood. Oxidative protein modifications in mitochondrial proteins from the heart and cerebrum of young (6.5 months) and old (27 months) rats were quantified and the effects of short-term and lifelong CR interventions were investigated. Mass spectrometry was leveraged to achieve an unbiased and comprehensive analysis of various types of oxidative postranslational modifications (oxPTMs). Contrary to the MFRTA, aging did not cause significant increases in mitochondrial protein oxidation in the heart and cerebrum. CR markedly diminished the overall level of oxPTMs in the heart, particularly in transmembrane proteins. Similarly, the level of oxidative modification of transmembrane proteins in cerebrum was reduced by CR, whereas it perplexingly increased in mitochondrial proteins. The absolute level of oxidized mitochondrial protein was always higher in the heart than in the cerebrum under all conditions. Carbonylation, a prevalent marker of protein oxidation and aging, increased in the heart with age and was notably reduced by CR. However, this trend was not consistent in cerebrum or for some other types of oxPTMs. Therefore, protein oxidation in the heart and cerebrum exhibits distinct responses to chronological aging and dietary interventions, with the latter exerting a stronger influence.

Calorie Restriction Attenuates Transcriptional Aging Signatures in White Matter Oligodendrocytes and Immune Cells of the Monkey Brain

During brain aging, terminally differentiated neuroglia exhibit metabolic dysfunction and increased oxidative damage, compromising their function. These cellular and molecular alterations impair their ability to maintain myelin sheath integrity, contributing to age-related white matter degradation. Calorie restriction (CR) is a well-established intervention that can slow biological aging and may reduce age-related metabolic alterations, thereby preserving the molecular function of aging glia. Here we present a single nucleus resolution, transcriptomics dataset evaluating the molecular profile of oligodendrocytes and microglia in the brain of aging rhesus monkeys following lifelong, 30% calorie restriction. Oligodendrocytes from CR subjects exhibited increased expression of myelin-related genes and showed enrichment in glycolytic and fatty acid biosynthetic pathways. In CR subjects, a subpopulation of oligodendrocytes upregulated cell adhesion gene, NLGN1 and were in closer proximity to axons. Microglia from CR subjects upregulated amino acid and peptide metabolism pathways and showed a reduced myelin debris signature. Our findings reveal cell-type specific transcriptional reprogramming in response to long term CR and highlight potential protective mechanisms against myelin pathology in the aging primate brain.

Aging–linked systemic lipid signature is reprogrammed by caloric restriction in rhesus monkeys

Caloric restriction (CR) without malnutrition delays aging in diverse species, including primates, with metabolic changes implicated in this process. To facilitate exploration of CR metabolism with aging, we developed a 15-minute LC-MS/MS metabolomics and lipidomics method, leveraging monophasic extractions and wide elution-strength solvents. We analyzed 494 plasma samples collected over 25 years from male and female rhesus monkeys (Macaca mulatta) on a Control or CR (30% restricted) diet. Quantitation of 359 biomolecules revealed that aging, followed by sex and diet, had the largest impact on metabolite abundances. In both sexes, aging was associated with significantly lower plasma levels of sphingomyelins (SMs) and higher levels of diglycerides (DGs) and triglycerides (TGs), each of which was opposed by CR. Sex dimorphism was evident by the increased abundance of phosphocholine (PC)-containing lipids in females. These results highlight the utility of a rapid metabolomics and lipidomics approach to elucidate complex biology in large-scale studies.

A Global Metabolomic and Lipidomic Landscape of Human Plasma Across the Lifespan

Xinru Liu, Tingting Liang, Rui Zhao, Mingming Zhu, Beibei Huang, Xiaobi Huang, Fang Ni

Understanding metabolic changes across the human lifespan is essential for addressing age-related health challenges. However, comprehensive metabolomic and lipidomic analyses, particularly in human plasma, remain underexplored. Herein, we performed untargeted metabolomics and lipidomics profiling of plasma collected from 136 individuals aged 0–84 years. This analysis reveals distinct metabolic signatures across life stages, with newborns displaying unique sphingosine (SPH) profiles, while aging was found to be characterized by elevated amino acid levels and lipid imbalances. Notably, we identified linear and nonlinear metabolic trajectories across the lifespan, highlighting critical transition points reflecting the key stages of metabolic reprogramming. By integrating these metabolic patterns, we developed an "aging clock" based on plasma metabolite profiling, thus providing a powerful tool to predict biological age. These findings offer new insights into the dynamic metabolic landscape of aging, paving the way for targeted interventions to improve healthspan and prevent age-related diseases.

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PREPRINT

A minor muscle stem cell population functions as metabolic Trojan horse fueling systemic aging by succinate induced epigenetic reprogramming

Inflammaging, the sustained chronic inflammation, is a hallmark of aging, yet its sustained activation mechanism remains elusive. Here, we identified muscle stem cells (MuSCs) as a driver of systemic inflammaging, evidenced by the multi-organ inflammation and aging phenotypes in MuSC specific Tet2 knockout mice. Tet2-Hdac11-Acod1-SDH axis maintained normal succinate level in MuSCs. Tet2 knockout disrupted this enzymatic cascade and led to succinate accumulation, fueling H4K31succ elevation to directly activate inflammatory gene transcription in MuSCs. The excess succinate was delivered to muscle fibers by sporadic fusion of Tet2 knockout MuSCs during muscle homeostasis, activated pro-inflammatory program, and transformed muscle to a persistent pro-inflammatory factor secretory organ, sustaining systemic inflammaging. Moreover, Tet2 was downregulated in aged MuSCs suggesting that this coupled metabolic-epigenetic mechanism was active in physiological aging. These findings reveal that a small subset of dysregulated MuSCs activate sustained whole-body inflammaging and multi-organ aging, providing new targets for rejuvenation strategy development.

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Targeting RhoA nuclear mechanoactivity rejuvenates aged hematopoietic stem cells

Biomechanical alterations contribute to the decreased regenerative capacity of hematopoietic stem cells (HSCs) upon aging. RhoA is a key regulator of mechanosignaling, but its role in mechanotransduction in stem cell aging remains unclear. Here we show that murine HSCs respond to increased nuclear envelope (NE) tension by inducing NE translocation of P-cPLA2, which cell-intrinsically activates RhoA. Aged HSCs experience physiologically higher intrinsic NE tension, but reducing RhoA activity lowers NE tension in aged HSCs. Feature image analysis of HSC nuclei reveals that chromatin remodeling is associated with RhoA inhibition, including restoration of youthful levels of the heterochromatin marker H3K9me2 and a decrease in chromatin accessibility and transcription at retrotransposons. Finally, we demonstrate that RhoA inhibition upregulates Klf4 expression and transcriptional activity, improving aged HSC regenerative capacity and lympho/myeloid skewing in vivo. Together, our data outline an intrinsic RhoA-dependent mechanosignaling axis, which can be pharmacologically targeted to restore aged stem cell function.

Reversing lysosomal dysfunction restores youthful state in aged hematopoietic stem cells

Aging impairs hematopoietic stem cells (HSCs), driving clonal hematopoiesis, myeloid malignancies, and immune decline. The role of lysosomes in HSC aging—beyond their passive mediation of autophagy—is unclear. We show that lysosomes in aged HSCs are hyperacidic, depleted, damaged, and aberrantly activated. Single-cell transcriptomics and functional analyses reveal that suppression of hyperactivated lysosomes using a vacuolar ATPase (v-ATPase) inhibitor restores lysosomal integrity and metabolic and epigenetic homeostasis in old HSCs. This intervention reduces inflammatory and interferon-driven programs by improving lysosomal processing of mitochondrial DNA and attenuating cyclic GMP-AMP synthase-stimulator of interferon gene (cGAS-STING) signaling. Strikingly, *ex vivo* lysosomal inhibition boosts old HSCs' *in vivo* repopulation capacity by over eightfold and improves their self-renewal. Thus, lysosomal dysfunction emerges as a key driver of HSC aging. Targeting hyperactivated lysosomes reinstates a youthful state in old HSCs, offering a promising strategy to restore hematopoietic function in the elderly.

Alpha-synuclein amyloids catalyze the degradation of ATP and other nucleotides

Claudio Castillo-Cáceres [1], Esteban Nova [2], Rodrigo Diaz-Espinoza [3]

Intracellular accumulation of alpha-synuclein amyloids is a main pathological hallmark in a subgroup of human neurodegenerative diseases called synucleinopathies. Cell death of energy-deprived dopaminergic neurons causes decreased dopamine levels, which underly many of the neurological symptoms in the most prevalent synucleinopathy, Parkinson's disease. Amyloid-mediated toxicity can proceed via gain-of-function through diverse pathways. In this work, we report that alpha-synuclein amyloids can degrade adenosine triphosphate in a catalytic fashion, producing adenosine diphosphate and adenosine monophosphate. Upon prolonged incubation, all adenosine triphosphate is irreversibly consumed. Furthermore, these amyloids can also degrade all other ribonucleotides with different efficiencies, including guanosine, cytidine, and uridine triphosphates. Our findings uncover a previously unknown gain-of-function for alpha-synuclein amyloids, which may have far reaching implications for ATP and nucleotide metabolism during neurodegeneration in Parkinson's disease and other synucleinopathies.

Modifying Glucose Metabolism Reverses Memory Defects of Alzheimer's Disease Model at Late Stages

Significant efforts have harvested a sophisticated understanding of Alzheimer's disease (AD) including amyloid beta (Aβ) cascade mechanisms, although effective treatment for reversing or stopping AD progression is not available. This study reports that ferul enanthate (SL), a novel derivative of active agents targeting brain microvessels, oxidative phosphorylation, and ATP generation can reverse the hippocampus-dependent spatial memory defects and reduce Aβ plaques in AD model mice (APP/PS1) at advanced stages. Spatial transcriptomics discovers that SL endows a cluster of genes expressing in Aging-AD-Rescue (AAR) pattern, which is prominent in hippocampal dendritic region where Aβ plaques are densely deposited. Furthermore, this AAR rule covers hippocampal Glut1 (glucose transporter 1) expression and ATP generation, which are further confirmed by immunoblotting or immunofluorescence studies. Our data demonstrate that SL can still reverse memory defects at advanced stages of AD mice by modifying aging-dependent multiple pathologies of AD, particularly promoting Glut1 expression and ATP generation.

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Genetic Associations with Longevity in a Calabrian Cohort:A Genome-Wide Study

Human longevity is a complex trait shaped by genetic background and population-specific factors. Calabria, a region in Southern Italy with a high prevalence of centenarians and relative genetic isolation, is a valuable model for investigating the genetic architecture of extreme survival. Here, we performed a genome-wide association study of longevity in 705 Calabrian individuals, comparing long-lived subjects to younger controls using a mixed-model approach that accounts for relatedness and population structure. We identified 267 candidate longevity-associated variants, including 23 suggestive genomic risk loci, of which one reached genome-wide significance. Although most loci did not replicate in external datasets, one intronic variant regulating proteasome-related gene expression was confirmed by meta-analysis. Gene- and pathway-based analyses highlighted biological processes central to aging, including proteostasis, DNA repair, telomere maintenance, apoptosis, insulin signaling, inflammation, and cancer-related pathways. Notably, established longevity loci such as *APOE* and *FOXO3* were not associated, underscoring population-specific genetic effects. Overall, our findings suggest that longevity in the Calabrian population arises from a combination of unique genetic influences and conserved aging-related mechanisms, providing new insights into the molecular basis of human lifespan extension.

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PREPRINT

Rare longevity-associated variants, including a reduced-function mutation in cGAS, identified in multigenerational long-lived families

Life expectancy has steadily increased in the last two centuries, while healthspan has been lagging behind. Survival into extreme ages strongly clusters within families which often exhibit a delayed onset of (multi)morbidity, yet the underlying protective genetic mechanisms are still largely undefined. We performed affected sib-pair linkage analysis in 212 sibships enriched for ancestral longevity and identified four genomic regions ($LOD_{max} \geq 3.0$) at *1q21.1*, *6p24.3*, *6q14.3*, and *19p13.3*. Within these regions, we prioritized 12 rare protein-altering variants in seven candidate genes (*NUP210L*, *SLC27A3*, *CD1A*, *CGAS*, *IBTK*, *RARS2*, and *SH2D3A*) located in longevity-associated loci. Notably, a missense variant in *CGAS* (rs200818241), was present in two sibships. Using human- and mouse-based cell models, we showed that rs200818241 reduced protein stability and attenuated activation of the canonical cGAS-STING pathway in a cell-type specific manner. This dampened signalling mitigated inflammation and delayed cellular senescence, mechanisms that may contribute to the survival advantage of *CGAS* variant carriers. Our findings indicate novel rare variants and candidate genes linked to familial longevity and highlight the cGAS-STING pathway as a potential contributor to the protective mechanisms underlying human longevity.

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Systemic LINE-1 RNA in Plasma Extracellular Vesicles Drives Neuroinflammation and Cognitive Dysfunction via cGAS-STING Pathway in Aging

Aging is characterized by systemic inflammation and progressive cognitive decline, yet the molecular pathways linking peripheral aging signals to central nervous system dysfunction remain elusive. Here, we identify plasma extracellular vesicle (EV)-derived long interspersed nuclear element-1 (LINE-1) RNA as a potent systemic aging factor mediating neuroinflammation and cognitive impairment in humans and mice. Plasma EV LINE-1 RNA levels markedly increase with age and strongly correlate with established brain aging biomarkers, including neurofilament light chain (NFL). Utilizing mouse models, we demonstrate that EVs from aged individuals penetrate the blood–brain barrier, deliver LINE-1 RNA to microglia, and initiate cGAS-STING signaling, leading to pronounced neuroinflammation, neuronal damage, and impaired cognition. Pharmacological blockade of LINE-1 reverse transcription by 3TC or inhibition of STING signaling with H151 significantly ameliorates these age-associated deficits. Notably, aged peripheral tissues, especially brain and lung, emerge as primary sources of pro-aging EVs enriched with LINE-1 RNA, revealing a novel mechanism of inter-organ communication in aging. Our findings position EV-derived LINE-1 RNA and its downstream cGAS-STING pathway as critical systemic drivers of brain aging, presenting promising therapeutic targets for mitigating cognitive decline and age-related neurodegenerative diseases.

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Platelet concentrate–derived extracellular vesicles promote adult hippocampal neurogenesis

Platelet-derived materials are emerging as promising, cell-free biotherapies for regenerative medicine. While platelet lysates have shown neuroprotective activity in preclinical models, the neurogenic potential of platelet concentrate-derived extracellular vesicles (pEVs) remains underexplored. Here, we evaluated the effects of human pEVs and heat-treated human platelet lysate (HPPL) on adult hippocampal neurogenesis using both an ex vivo neurosphere assay and an in vivo intranasal administration model. pEVs selectively enhanced dentate gyrus (DG)-derived neurosphere growth, even in the absence of exogenous growth factors, and were internalized by neural precursors. In vivo, short-term pEV delivery increased EdU^+ proliferating cells in the DG, while long-term administration (28 days) elevated the proportion of newborn mature neurons. By contrast, HPPL primarily promoted early neurogenesis by expanding immature DCX^+ neurons. Quantitative proteomics of DG tissue after pEV treatment revealed 111 differentially expressed proteins, with enrichment in pathways related to oxidative phosphorylation, Notch4 signaling, myelination, and MHC class I-mediated antigen presentation. Downregulated proteins included cytoskeletal and translation-related regulators, suggesting a shift toward neuronal differentiation and circuit integration. Biophysical characterization confirmed the purity and vesicular nature of pEVs, with a defined protein cargo including immune modulators and ECM-interacting molecules such as CD44, lymphatic vessel endothelial hyaluronan receptor 1 (LYVE1), and complement proteins. These findings identify allogeneic pEVs as multifunctional agents that modulate neural precursor cell fate and brain tissue remodeling through coordinated metabolic and immunoregulatory mechanisms. This work supports the translational potential of pEV-based therapeutics for promoting hippocampal neurogenesis and cognitive repair in neurodegenerative and age-related brain disorders.

Control of aging-associated neurodegeneration via hypothalamic extracellular vesicles containing parathymosin

Aging-associated neurodegeneration underlies various neurological diseases; however, the neurocrine basis remains poorly understood. Here, we investigate the role of parathymosin (PTMS), a secretory protein with nuclear functions that has recently been identified as a circulating factor in the brain. The results show that loss of PTMS is sufficient to cause severe, age-dependent neurodegeneration and reduced lifespan, whereas hypothalamic PTMS gain of function counteracts aging-associated brain disorders and extends lifespan. PTMS is present in hypothalamic extracellular vesicles (EVs), particularly in subpopulations released by hypothalamic neural stem/progenitor cells (htNSCs). These htNSC-derived EVs carry small nuclear and nucleolar RNAs in a PTMS-associated manner to protect recipient neurons from DNA damage. Therapeutically, these htNSC-derived EVs provide a strong effect against neurodegenerative disorders associated with PTMS deficiency in mouse models, including Alzheimer's disease (AD)-like phenotypes in the 5xFAD model. In conclusion, PTMS possesses anti-neurodegenerative properties, and PTMS-containing hypothalamic EVs are significant in combating aging-associated neurodegenerative diseases.

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Rejuvenation of white adipose tissue in a longitudinal heterochronic transplantation model

Exposure to a younger system can induce organismal rejuvenation, yet whether all tissues can be rejuvenated and by what mechanisms remains understudied. We performed heterochronic and isochronic transplantation of subcutaneous white adipose tissue (WAT) between young and old mice and longitudinally tracked changes in biological age. Transplantation accelerated tissue aging, and the molecular age of grafts shifted toward that of the host. Most importantly, old WAT was rejuvenated in a young body. Epigenetic and transcriptomic clocks revealed a reduction of predicted age, accompanied by coordinated activation of canonical and previously unrecognized thermogenic pathways. Molecular rejuvenation was further supported by architectural changes toward a youthful state, including reduced lipid droplet size and decreased cellular heterogeneity. Mitochondrial abundance and morphology remained unchanged, while collagen deposition increased. These results demonstrate that WAT biological age is partially reversible and identify molecular and cellular features underlying its rejuvenation

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PREPRINT

Maximal human lifespan in light of a mechanistic model of aging

Ben Shenhar, Shachaf Frenkl, Tomer Levy, Uri Alon

Why has maximal human lifespan barely changed in the past two centuries? To understand this we make a mechanistic link between cellular damage, survival curves, and maximum lifespan using a validated stochastic model of damage accumulation and extensive human data. We show that maximal lifespan is set mainly by damage production and clearance rates, as in progeroid syndromes. In contrast, lifestyle factors such as exercise, nutrition, and sleep chiefly reduce stochastic noise and raise the damage level compatible with survival, shifting the median but not the maximum. Similar constraints arise in other mortality models. Our analysis predicts that lifestyle can extend maximal lifespan by at most ~1 year; substantial gains will require directly perturbing damage production or removal, suggesting specific molecular targets.

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Aging, matrix metalloproteinase imaging, and survival prospects in aortic aneurysm

Methods AA development and animal survival were monitored for 28 days after Angiotensin (Ang)-II infusion in 8-10-week-old (young) and >51-week-old (old) *Apoe*$^{-/-}$ mice. Aortic MMP activation was quantified by PET/CT using an MMP-targeted tracer, ^{64}Cu-RYM2, at baseline and 1 week after Ang II infusion. MMP activity and expression were quantified by tissue zymography and quantitative reverse transcription polymerase chain reaction, and compared between different segments of the aorta in young and old animals, and before and after Ang II infusion.

Results Old animals' survival to 28 days was significantly lower than that of young Ang-II-infused *Apoe*$^{-/-}$ mice ($P < 0.05$). ^{64}Cu-RYM2 PET/CT showed significantly higher aortic MMP activation before and 1 week after Ang-II infusion in old compared to young *Apoe*$^{-/-}$mice. The ^{64}Cu-RYM2 signal was significantly higher in animals that did not survive 28 days than those that did ($P < 0.01$). MMP activity significantly increased by 4 days after Ang-II infusion, when dissection was found in a subset of *Apoe*$^{-/-}$ mice; and was significantly higher in the dissected, compared to adjacent, apparently normal, segments of the aorta. MMP activity was also significantly higher in the ascending thoracic aorta of untreated young and old mice, as well as of Ang-II-treated *Apoe*$^{-/-}$mice (which was associated with significantly higher *Mmp2* gene expression), and of old wild-type mice.

Conclusion Aging is associated with increased MMP activity along the aorta and worse AA survival. MMP-targeted molecular imaging can inform the aneurysm survival prospects. Selective MMP inhibitors and tracers may help prevent and track aneurysm growth, dissection, and rupture.

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Induction of ferroptotic and amyloidogenic signatures linked to Alzheimer's disease by chemically distinct air pollutants

Air pollution (AirP) exposure is associated with increased Alzheimer's disease (AD) risk, yet AirP is chemically heterogeneous, complicating identification of shared pathogenic drivers. We examined acute cortical responses to two metal-rich AirP sources, diesel exhaust particles (DEP) and World Trade Center (WTC) dust, and compared them to woodsmoke (WS), a particulate exposure with low metal content. DEP and WTC elicited highly convergent transcriptional responses, sharing over 1200 differentially expressed genes linked to inflammation, ferroptosis, neuronal remodeling, and amyloid processing. These changes were accompanied by impaired antioxidant activity and increased lipid peroxidation within lipid rafts, a membrane microdomain critical for amyloid processing, resulting in increased Aβ generation. In contrast, WS produced a distinct transcriptional signature and failed to induce ferroptotic priming or lipid peroxidation, consistent with its low metal composition. Together, these findings implicate metals as a shared driver linking diverse AirP exposures to amyloidogenic vulnerability and elevated AD risk.

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PREPRINT

Identification of chemicals targeting dementia genes and pathways in the Comparative Toxicogenomics Database

Scarlet Cockell, Sean M. Harris, Rachel K. Morgan, Gary J. Patti, Erin B. Ware, Kelly M. Bakulski

Introduction Dementia is a public health challenge and exposures likely contribute to risk, though many have not been evaluated. We screened chemicals for enrichment with dementia genes and related pathways.

Methods We obtained gene lists from the Comparative Toxicogenomics Database for 1,008 chemicals and nine dementia-related pathways (e.g., Alzheimer's disease, tauopathies). We tested pairwise chemical-dementia gene enrichment using Fisher's exact tests and proportional reporting ratios (PRR), accounting for multiple comparisons with false discovery rate (FDR<1×10^{-6}).

Results Of the chemicals tested, 742 (73.6%) were enriched for at least one dementia pathway and 15 with all nine pathways, including benzo(a)pyrene, ethanol, paraquat, and particulate matter. We observed 295 chemicals enriched for Alzheimer's disease, including sodium arsenite (PRR = 57.9) and 305 enriched for tauopathies, including bisphenol A (PRR=37.7).

Discussion We identified chemicals enriched for dementia pathways, suggesting broad classes of chemicals contribute to dementia.

NAD^+ restores proteostasis through splicing–dependent autophagy

Ruixue Ai [1], Evandro F Fang [1 2]

Autophagy preserves neuronal integrity by clearing damaged proteins and organelles, but its efficiency declines with aging and neurodegeneration. Depletion of the oxidized form of nicotinamide adenine dinucleotide (NAD^+) is a hallmark of this decline, yet how metabolic restoration enhances autophagic control has remained obscure. Meanwhile, alternative RNA splicing errors accumulate in aging brains, compromising proteostasis. Here, we identify a metabolic - transcriptional mechanism linking NAD^+ metabolism to autophagic proteostasis through the NAD^+ -EVA1C axis. Cross-species analyses in *C. elegans*, mice, and human samples reveal that NAD^+ supplementation corrects hundreds of age- or Alzheimer-associated splicing errors, notably restoring balanced expression of EVA1C isoforms. Loss of EVA1C impairs the memory and proteostatic benefits of NAD^+, underscoring its essential role in neuronal resilience. Mechanistically, NAD^+ rebalances EVA1C isoforms that interact with chaperones BAG1 and HSPA/HSP70, reinforcing their network to facilitate chaperone-assisted selective macroautophagy and proteasomal degradation of misfolded proteins such as MAPT/tau. Thus, NAD^+ restoration coordinates RNA splicing fidelity with downstream proteostatic systems, establishing a metabolic - transcriptional checkpoint for neuronal quality control. This finding expands the paradigm of autophagy regulation, positioning metabolic splice-switching as a crucial mechanism to maintain proteostasis and suggesting new strategies to combat aging-related neurodegenerative diseases.

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Long-term high-protein diet intake accelerates adipocyte senescence through macrophage CD38-mediated NAD^+ depletion

High-protein (HP) diets are widely adopted in Western societies for body-weight management; yet, they exacerbate senescence-associated metabolic deterioration, posing an unresolved pathophysiological conundrum. Here, we demonstrate that long-term HP intake mediates adipocyte-specific NAD^+ depletion and mitochondrial dysfunction in white adipose tissue (WAT). Single-nucleus transcriptomic analyses revealed adipocyte-restricted senescence signatures in HP-fed mice. Mechanistically, HP intake triggers macrophage-specific upregulation of CD38 (a key NAD^+ hydrolase), which depletes adipocyte NAD^+ pools and thereby accelerates cellular senescence. Restoration of NAD^+ levels, either via supplementation with NAD^+ precursor or pharmacological inhibition of CD38 activity, alleviated the senescence-associated metabolic sequelae induced by HP diets. Our findings establish macrophage-adipocyte NAD^+ crosstalk as a central axis linking dietary protein excess to WAT aging, providing actionable targets for the prevention and treatment of age-related metabolic disorders.

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PREPRINT

Multi-omics Analysis of Human Blood Cells Reveals Unique Features of Age-associated Type2 CD8 Memory T cells

Aging impacts immune function, but the mechanisms driving age-related changes in immune cell subsets remain unclear. To explore age-dependent changes in immune cell populations, we analyzed human peripheral blood mononuclear cells (PBMCs) from a cohort of healthy donors aged 20–82 years using a 36-color spectral flow cytometry panel focused on T cells. We identified a unique population of memory CD8 T cells, which lack CXCR3 and produce a Th2-like cytokine response, accumulate with age. We discovered an age-dependent bias in naïve CD8 T cells toward Th2 cytokine production, accompanied by transcriptional and epigenetic changes supporting this phenotype. Moreover, health outcome association analysis linked the accumulation of these unique CXCR3- central memory CD8 T cells to asthma, chronic liver conditions, and type 2 diabetes. Together, our results support the model that an age-dependent drift in epigenetic regulation towards a Th2-like phenotype drives a pathogenic Th2-like immune population.

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PREPRINT

Senescent CD8 T Effector Memory Cells are Functionally Impaired, Enriched in Aging and Disease, and a Barrier to Immunotherapy

Senescent cells play important roles in various biological processes that promote fitness and health, however, their timely elimination by immune cells is critical to maintain tissue homeostasis and prevent disease. Despite this, senescent cells progressively accumulate systemically with age, suggesting that certain immune cells also become senescent and dysfunctional during aging. Supporting this, we previously demonstrated that CD8 T cells, immune cells capable of targeting senescent cells, increasingly develop characteristics of senescence with advancing age in humans. Here, we further characterized the senescence state of human SA-βGal-expressing CD8 T effector cells, their functional capabilities, and their involvement in aging and disease. Single-cell RNA sequencing revealed that SA-βGal-expressing CD8 T cells with unique transcriptional signatures develop in all stages of T cell differentiation, including in effector memory (EM) T cells. SA-βGal-expressing CD8 T_{EM} cells expressed various classical markers of senescence and were significantly impaired in their ability to proliferate, produce cytokines, and eliminate senescent human stromal cells, compared to CD8 T_{EM} cells with low SA-βGal activity. Gene signatures of senescent SA-βGal-expressing CD8 T_{EM} cells were enriched in CD8 T cells from older human donors, patients with age-related disorders, cancer, and smokers. Furthermore, our results demonstrate that T cell senescence is distinct from and dominant over T cell exhaustion, limiting the response of CD8 T_{EM} cells to immunotherapy. Collectively, our study demonstrates that the senescence state impairs the functions of CD8 T_{EM} cells and reveals the involvement of senescent and dysfunctional CD8 T_{EM} cells in aging, disease, exposure to toxins, and responses to immunotherapy.

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PREPRINT

Integrative transcriptomic identification of cellular senescence beyond marker limitations

Jing Lu, İsmail Güderer, Tayyaba Alvi, Mark Olenik, Handan Melike Dönertaş

Cellular senescence lacks a universal marker and varies across cell types, tissues, and stressors, complicating identification. Using SPiDER SA-β-gal labeled single-cell RNA-seq from regenerating mouse muscle, we found that curated gene sets show opposing enrichment patterns in experimentally defined senescent cells, suggesting apparent concordance in prior studies may reflect circular validation. Machine learning classifiers outperformed marker-centric approaches by capturing coordinated transcriptional features largely absent from differentially expressed genes. These features traced senescence progression, positioning senescent cells at late pseudotime with reduced transcriptional entropy. Ligand-receptor analysis identified IGF signaling as a directional axis of secondary senescence from senescent to non-senescent cells. When applied to bulk RNA-seq and an independent aging dataset, the classifier detected age-associated senescence patterns while the entropy-senescence relationship held across most cell types. These findings demonstrate that transcriptome-based classification provides a robust alternative to marker-centric readouts while enabling mechanistic hypothesis generation.

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PREPRINT

Exploring molecular signatures of senescence with markeR, an R toolkit for evaluating gene sets as phenotypic markers

Many biological processes, including cellular senescence, manifest as diverse phenotypes that vary across cell types and conditions. In the absence of single, definitive markers, researchers often rely on the expression of sets of genes to identify these complex states. However, there are multiple ways to summarise gene set expression into quantitative metrics (*i.e.*, signatures), each with its own strengths and limitations, and we know of no consensual framework to systematically evaluate their performance across datasets. We therefore developed markeR (https://bioconductor.org/packages/markeR), an open-source, modular R package that evaluates gene sets as phenotypic markers using various scoring and enrichment-based approaches. markeR generates interpretable metrics and intuitive visualisations that enable benchmarking of gene signatures and exploration of their associations with chosen study variables. As a case study, we applied markeR to 9 published senescence-related gene sets across 25 RNA-seq datasets, covering 6 human cell types and 12 senescence-inducing conditions. There was wide variability in gene set performance, as some signatures (*e.g.*, SenMayo) were robust senescence markers across contexts, while others (*e.g.*, those from MSigDB), performed poorly as such. We also used markeR to analyse gene expression in 49 GTEx tissues, revealing tissue- and age-related diberences in senescence-associated signals. Together, these findings emphasise the dibiculty of characterising molecular phenotypes and demonstrate the potential of markeR in facilitating the systematic evaluation of gene sets in various biological contexts.

Mitochondrial RNA cytosolic leakage drives the SASP

Senescent cells secrete proinflammatory factors known as the senescence-associated secretory phenotype (SASP), contributing to tissue dysfunction and aging. Mitochondrial dysfunction is a key feature of senescence, influencing SASP via mitochondrial DNA (mtDNA) release and cGAS/STING pathway activation. Here, we demonstrate that mitochondrial RNA (mtRNA) also accumulates in the cytosol of senescent cells, activating RNA sensors RIG-I and MDA5, leading to MAVS aggregation and SASP induction. Inhibition of these RNA sensors significantly reduces SASP factors. Furthermore, BAX and BAK play a key role in mtRNA leakage during senescence, and their deletion diminishes SASP expression in vitro and in a mouse model of Metabolic Dysfunction-Associated Steatohepatitis (MASH). These findings highlight mtRNA's role in SASP regulation and its potential as a therapeutic target for mitigating age-related inflammation.

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PREPRINT

Senescent cells secrete chromatin components via senescence-associated extracellular particles

Senescent cells influence their surroundings through the senescence-associated secretory phenotype (SASP), an assortment of secreted molecules and macromolecular complexes. Among SASP's intracellular drivers are cytoplasmic chromatin fragments (CCFs), nuclear-derived DNA that activates the pro-inflammatory cGAS/STING pathway. While autophagy contributes to CCFs degradation, the full repertoire of CCF fates and signaling functions remains unclear. Here, we show that senescent cells release CCF components, γH2AX and double-stranded DNA (dsDNA), into the extracellular space via an ESCRT-independent multivesicular body pathway. Secreted CCF components localize to extracellular particles exhibiting an unusual "popcorn"-like morphology, distinct from canonical small extracellular vesicles. Notably, inhibition of autophagy enhances secretion of CCF components and particles, suggesting an inverse relationship between intracellular clearance and extracellular release. A fraction of CCF-containing extracellular particles activates cGAS-STING signaling in non-senescent proliferating cells and is enriched in the circulation of aged mice, pointing to a previously unrecognized mode of extracellular signaling by senescent cells.

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PREPRINT

$p16^{INK4A}$ expression induces paracrine senescence via small extracellular vesicles

Senescent cells are characterized by the expression of the cell cycle inhibitor and biomarker of aging, $p16^{INK4A}$, and the capacity to modify the microenvironment through the senescence-associated secretory phenotype (SASP). Senescent cells accumulate in physiological and pathological conditions, including aging. In spite of this, fibroblasts ectopically expressing $p16^{INK4A}$ do not release a SASP nor communicate with the microenvironment. Here, we find that human primary fibroblasts expressing $p16^{INK4A}$ release more small extracellular vesicles (sEV) as part of the SASP than proliferating cells. In addition, we show that sEV isolated from $p16^{INK4A}$ cells are able to mediate paracrine senescence by inducing a growth arrest and DNA damage response in proliferating cells albeit not stimulating the expression of IL-8. Furthermore, we show the transmission of paracrine senescence via sEV is conserved in two cellular models of ageing: expression of progerin, mimicking an accelerated form of ageing, and inducing telomere shortening using a dominant negative mutant. Importantly, sEV isolated from fibroblasts derived from old donors also induce paracrine senescence in fibroblasts derived from young donors. In conclusion, our data indicate that sEV released by senescent and aging cells are an important mechanism of intercellular communication and could potentially explain tissue dysfunction in aging.

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Senolytic-Resistant Senescent Cells Have a Distinct SASP Profile and Functional Impact: The Path to Developing Senosensitizers

The senescent cell (SC) fate is linked to aging, multiple disorders and diseases, and physical dysfunction. Senolytics, agents that selectively eliminate 30%–70% of SCs, act by transiently disabling the senescent cell antiapoptotic pathways (SCAPs), which defend those SCs that are proapoptotic and pro-inflammatory from their own senescence-associated secretory phenotype (SASP). Consistent with this, a JAK/STAT inhibitor, Ruxolitinib, which attenuates the pro-inflammatory SASP of senescent human preadipocytes, caused them to become "senolytic-resistant". Administering senolytics to obese mice selectively decreased the abundance of the subset of SCs that is pro-inflammatory. In cell cultures, the 30%–70% of human senescent preadipocytes or human umbilical vein endothelial cells (HUVECs) that are senolytic-resistant (to Dasatinib or Quercetin, respectively) had increased $p16^{INK4a}$, $p21^{CIP1}$, senescence-associated β-galactosidase (SAβgal), γH2AX, and proliferative arrest similarly to the total SC population (comprising senolytic-sensitive plus-resistant SCs). However, the SASP of senolytic-resistant SCs entailed less pro-inflammatory/apoptotic factor production, induced less inflammation in non-senescent cells, and was equivalent or richer in growth/fibrotic factors. Senolytic-resistant SCs released less mitochondrial DNA (mtDNA) and more highly expressed the anti-inflammatory immune evasion signal, glycoprotein non-melanoma-B (GPNMB). Transplanting senolytic-resistant SCs intraperitoneally into younger mice caused less physical dysfunction than transplanting the total SC population. Because Ruxolitinib attenuates SC release of proapoptotic SASP factors, while pathogen-associated molecular pattern factors (PAMPs) can amplify the release of these factors rapidly (acting as "senosensitizers"), senolytic-resistant and senolytic-sensitive SCs appear to be interconvertible.

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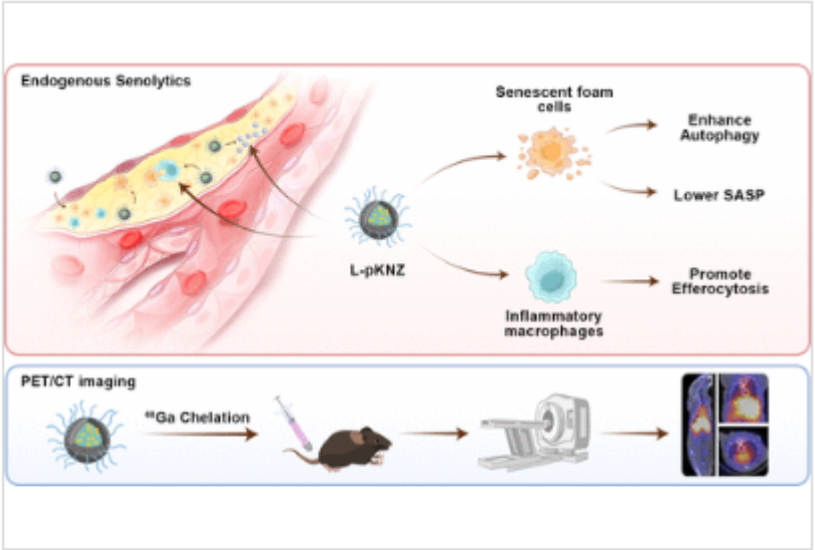
IFN–Mediated Bronchial Epithelium Cellular Senescence in Chronic Obstructive Pulmonary Disease

Cellular senescence has been implicated in the pathogenesis of chronic obstructive pulmonary disease (COPD). The mechanisms of senescence in the bronchial epithelium, however, remain largely unknown. In this study, we aimed to elucidate whether cellular senescence in COPD epithelial cells contributes to the pathogenesis of the disease and investigated the potential molecular mechanisms involved. Single-cell RNA sequencing was performed on well-differentiated primary bronchial epithelial cells from patients with COPD and healthy subjects. We evaluated the abundance and distribution of senescence markers in key epithelial differentiated subtypes and senescence-associated secretory phenotype involved in airway epithelial dysfunction. The effects of IFN-pathway inhibitors on cellular senescence were also investigated. There was increased expression of cellular senescence genes in the COPD cohort, which was predominantly in basal and club cells. Enhanced expression of cellular senescence markers, p16 and p21, was observed in COPD cultures, which was histologically confirmed in the lung tissue of patients with COPD. There was also a notable increase in IFN-β and IFN-γ. Senescence-associated secretory phenotype productions were increased in COPD and were attenuated by JAK-STAT or cGAS-STING pathway inhibitors (baricitinib or C-176). These inhibitors also effectively suppressed expression of senescence markers. COPD bronchial epithelium displays a senescence-driven phenotype which is mediated by Type I/II IFNs. Inhibition of JAK-STAT or STING-cGAS IFN pathways may represent targets to alleviate cellular senescence and chronic inflammation in COPD.

In Situ Reprogramming of Senescent Microenvironment via Augmentation of Endogenous Senolytic Actions for Advanced Atherosclerosis Management



Advanced atherosclerosis (AS) poses substantial residual risk of life-threatening cardiovascular disease, even with optimized lipid-lowering therapies. Histopathological evaluation of clinically obtained specimens revealed that advanced plaques developed a distinct senescent microenvironment compared to early stage lesions, and senescent foam cells (FCs) are the culprits in creating the pathological microenvironment via initiating senescence-propagating crosstalk with multiple vascular cells. Herein, we synthesized a zeolitic imidazolate framework-8 (ZIF-8)-based nanomedicine denoted as L-pKNZ. Unlike conventional senolytic agents that primarily induce cellular apoptosis, L-pKNZ activates FC autophagy and enhances macrophage efferocytosis. This strategy established an endogenous senolytic system to relieve FC overload while simultaneously reprogramming the senescent microenvironment. Results from multiomics analysis aligned with outcomes from in vitro/in vivo experiments, all in favor of vascular rejuvenation and AS amelioration. Critically, we successfully radiolabeled L-pKNZs with the radionuclide ^{68}Ga, which allowed noninvasive in vivo imaging of the senescent microenvironment with micro-PET/CT. Overall, this study provides a versatile theranostic platform with broad implications for age-related diseases.

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Prodrug nanoplatform for triggering ferroptosis to eliminate senescent cells in age-associated pathologies

Accumulation of senescent cells is associated with aging and age-related diseases. However, current clearance therapies targeting senescent cells are often limited by low efficiency, poor specificity, and insufficient penetration. Here we develop a nano-platform composed of a probe (GD) that can be specifically activated by senescent cells, a photosensitizer (Ce6), and a peptide (HK) for targeting ferritin, named HK-PCGC. We show that upon entering senescent cells, GD is activated by high levels of β-galactosidase, releasing fluorescence to excite Ce6. Ce6 then generates reactive oxygen species to eliminate these cells. Additionally, we find that under the guidance of the peptide HK, our system degrades ferritin to trigger ferroptosis, further eliminating senescent cells. Collectively, we demonstrate that HK-PCGC can effectively eliminate senescent cells, reduce the senescence-associated secretory phenotype, and safely improve the physical fitness of aged mice. This study integrates senescent cell responsiveness, laser-free photodynamic therapy, and induction of ferroptosis, offering a potential approach for delaying aging.

Reduction of solid tumors by senescent cell immunization

Results

SenoVax™ was created by pulsing DC with cell lysate from senescent fibroblasts, producing DCs that expressed co-stimulatory molecules, stimulated T cell proliferation, and expressed the senescence antigen p16. SenoVax™ induced prophylactic and therapeutic tumor regression in LLC primary and metastatic murine tumor models. T cell proliferative and cytokine recall responses towards senescent cells but not to control stromal cell pulsed DCs were detected in vaccinated mice. Additionally, reduction in senescence associated biomarkers IL-11, IL-6, IL-23 receptor, and YLK-40 were observed. Adoptive transfer experiments revealed a role for CD8+ T cells in transplanting protection. When SenoVax™ was administered in combination with anti-PD-L1 or anti-CTLA-4 antibodies, the data showed synergistic effects in reducing tumor growth. SenoVax™ also demonstrated reduction of GL281 glioma, Pan01 pancreatic cancer, and 4T1 breast cancer cell growth. No significant activation of complement or induction of autoantibodies was observed.

Conclusion

Vaccination with DC pulsed senescent cells resulted in reduction of tumor growth in a CD8+ T cell and interferon gamma-associated manner in lung cancer as well as other tumor models. The data provide mechanistic support for advancement of senolytic immunotherapy as a novel form of cancer therapy.

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PREPRINT

Systemic administration of PD-L1 blocking antibodies leads to removal of senescent microglia

Yuliya Androsova, Alexander Kertser, Hannah Partney, Bar Nathansohn, Angham Ibraheem, Miguel Abellanas, Tommaso Croese, Tomer Meir Salame, Hagay Akiva, Valery Krizhanovsky, Michal Schwartz

Senescent microglia develop during aging and Alzheimer's disease (AD), driving chronic neuroinflammation. Here we hypothesized that the previously observed disease-modifying effects of PD-1/PD-L1 blockade occur through clearance of senescent microglia. Using CyTOF, we found that a single systemic anti-PD-L1 injection leads to rapid elimination of senescent microglia in 5xFAD and aged wild-type mice, independently of Fc effector function, while increasing homeostatic microglia. These findings suggest that immune rejuvenation via PD-L1 blockade promotes disease modification in AD through senescent-microglial elimination.

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Abrogation of aberrant glycolytic interactions eliminates senescent cells and alleviates aging-related dysfunctions

Cellular senescence is deeply involved in physiological homeostasis, development, tissue repair, aging, and diseases. Senescent cells (SnCs) accumulate in aged tissues and exert deleterious effects by secreting proinflammatory molecules that contribute to chronic inflammation and aging-related diseases. We revealed that an aberrant interaction between glycolytic PGAM1 and Chk1 kinase is augmented in SnCs associated with increased glycolysis, whose byproduct, lactate, promotes this binding in a noncell autonomous manner. The pseudo-Warburg effect of SnCs with enhanced PPP (pentose phosphate pathway) activity is maintained by HIF-2α phosphorylation by Chk1 and subsequent upregulation of glycolytic enzymes, creating a vicious cycle reprogramming the glycolytic pathway in SnCs. HIF-2α also activates FoxM1 expression, which transcriptionally suppresses proapoptotic profiles, including BIM, and upregulates DNA repair machineries in SnCs. FoxM1 thus supports the genomic integrity and survival capacity of SnCs during their glycolytic changes. Chemical abrogation of PGAM1-Chk1 binding reverts these phenotypes and eliminates SnCs through senolysis. Inhibition of the PGAM1-Chk1 interaction improves physiological parameters during aging and inhibits lung fibrosis in mouse models. Our study highlights a novel pathway contributing to the metabolic reprogramming of SnCs and how the use of a new senolytic molecule that targets the PGAM-Chk1 interaction creates a specific vulnerability of those cells to potentially fight age-related diseases.

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PREPRINT

Targeting the senescence-associated immune checkpoint GD3 ganglioside extends healthspan and blunt age-related diseases with sex-specific benefits

Iryna Moskalevska, Larisa Okorokova, Raphaël Rousset, Thierry Juhel, Eric Gilson, Bérengère Dadone-Montaudie, Laurence Bianchini, Gaël Cristofari, Julien Cherfils-Vicini

The accumulation and impact of senescent cells in age-related diseases are increasingly characterized. However, the mechanisms underlying their accumulation and their causative role in age-associated pathologies remain poorly understood. We recently demonstrated that senescent cells can evade immune surveillance by regulating the expression of cell surface molecules such as the disialylated ganglioside GD3, which acts as a senescence-associated immune checkpoint (SIC) [1–3]. Targeting GD3 therefore represents a novel therapeutic opportunity for age-related diseases. Here, we examined the effects of short-term anti-GD3 antibody treatment in mid-life on aging and age-related diseases in male and female mice, revealing striking sex-specific benefits. Treatment improved healthspan, survival (+20%) and reduced non-cancer mortality in males, while in females it reduced cancer-specific mortality without significantly affecting overall survival. Anti-GD3 treatment also mitigated fibrosis in lung, liver, and kidney tissues with distinct sex-dependent responses. Importantly, these benefits persisted for over a year after treatment cessation. These findings suggest that GD3-targeted therapy holds promise as a precision approach for treating age-related diseases, with therapeutic outcomes that depend critically on biological sex.

Senolytic Treatment With Dasatinib and Quercetin Reshapes Influenza-Specific CD8 T Cell Responses During Infection in Aged, Vaccinated Mice

Older adults are disproportionately affected by infectious diseases like influenza (flu) due to immune declines and poor vaccine responses. Senolytics have been shown to improve various age-related conditions and positively influence infection outcomes, yet their potential to enhance vaccine responses has not yet been explored. Here, we evaluated the potential of senolytic combination Dasatinib (D) and Quercetin (Q) treatment prior to influenza vaccination to potentiate immune responses in aged mice. D + Q had minimal impact on overall vaccination and flu outcomes in vaccinated mice, including viral load and lung pathology. However, we observed altered CD8 T cell immunodominance and increased serum total PR8 (whole flu) IgG antibodies in D + Q treated vaccinated aged mice during infection. These findings reveal a new aspect of immunomodulation with senolytics.

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PREPRINT

Influenza A infection accelerates disease-associated microglia formation during physiological aging

Severe pneumonia is associated with an increased risk of cognitive decline and dementia, particularly in the elderly. Changes in microglia, the most abundant immune cell population in the brain, are also associated with cognitive decline and dementia, including the emergence of a transcriptional cell state referred to as disease-associated microglia (DAM). We sought to test the hypothesis that non-neuroinvasive influenza A virus (IAV) pneumonia results in transcriptional responses in brain microglia that drive premature expansion of DAM. Using bulk and single-cell RNA-sequencing, metabolomics, and spatial transcriptomics, we profiled neuroimmune populations in young, middle-aged, and old male mice during IAV infection and recovery. We observed an increased abundance of DAM, interferon-responsive microglia (IRM), CD4+ T cells, and CD8+ T cells in white matter regions beginning in middle age and persisting in old animals, irrespective of IAV infection. DAM exhibited a metabolic shift toward aerobic glycolysis with disrupted TCA cycling, citrulline depletion, and an elevated itaconate/α-ketoglutarate ratio. Spatial transcriptomic profiling of the human middle frontal gyrus (MFG) in normal agers, SuperAgers, and patients with dementia revealed an analogous accumulation of DAM and CD8+ T cells in white matter. IAV pneumonia induced a transient immunosenescent-like response in microglia, marked by glucocorticoid-responsive gene expression and *Ccnd3* upregulation. In response to IAV pneumonia, DAM expanded in middle-aged mice, whereas old mice were elevated at baseline and were largely unaffected by IAV infection. The age-related expansion of DAM was unaffected by pharmacological depletion and repopulation of microglia with a CSF1R antagonist or genetic gain or loss of function of the phagocytic receptor MERTK, suggesting the DAM phenotype is driven by the CNS microenvironment, rather than cell-intrinsic mechanisms. Our findings suggest that IAV pneumonia induces an acute immunosenescence response in microglia and accelerates the age-dependent expansion of DAM in white matter.

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PREPRINT

Flu Virus Infection in Juvenile Mice Leads to Lifelong Multi-Organ Damage and Parkinsonian Pathological Changes in Aging

The widespread prevalence of Long COVID underscores the potential for viral infections to exert prolonged effects on hosts long after initial recovery. Despite this recognition, the long-term and even lifelong consequences of viral infections remain poorly understood. In this study, we infected juvenile mice with influenza viruses and systematically examined the lifelong effects (from 4 to 450 days post-infection) of these infections. Pathological analysis revealed persistent lifelong damage in multiple organs, including chronic lung inflammation and fibrosis, along with significant cardiac and renal pathology. Viral infection led to substantial neuronal loss in key brain regions of mice (hippocampal CA1, CA3, and striatum) during middle and old age. Strikingly, we identified two hallmark pathological features of Parkinson's disease - dopaminergic neuron degeneration and Lewy body–like α-synuclein inclusions - in middle and aged infected mice. Transcriptomic profiling demonstrated sustained upregulation of inflammation-related genes in both lung and blood tissues, correlating with observed pathological changes. Lung-derived secreted proteins, encoded by differentially expressed genes, may mediate cross-organ communication affecting cardiac, renal, and neurological function. Brain transcriptome analysis at three months post-infection revealed downregulation of neurodevelopmental genes, potentially contributing to subsequent neuronal loss and Parkinsonian pathology. These findings collectively suggest that pulmonary influenza infection can induce systemic multi-organ effects through both secretory pathways and chronic inflammatory responses. The study offers crucial insights for developing more effective strategies to prevent and manage infectious diseases and their long-term sequelae.

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Dietary restriction reprograms CD8$^+$ T cell fate to enhance anti-tumour immunity and immunotherapy responses

Reducing calorie intake through dietary restriction (DR) slows tumour growth in mammals, yet the underlying mechanisms are poorly defined. Here, we show that DR enhances anti-tumour immunity by optimizing CD8$^+$ T cell function within the tumour microenvironment (TME). Using syngeneic xenograft tumour models, we found that DR induces a profound reprogramming of CD8$^+$ T cell fate in the TME, favouring the expansion of effector T cell subsets with enhanced metabolic capacity and cytotoxic potential, while limiting the accumulation of terminally exhausted T cells. This metabolic reprogramming is driven by enhanced ketone body oxidation, particularly β-hydroxybutyrate (βOHB), which is elevated in both the circulation and tumour tissues of DR-fed mice. βOHB fuels T cell oxidative metabolism under DR, increasing mitochondrial membrane potential and tricarboxylic acid cycle-dependent pathways critical for T cell effector function, including acetyl-CoA production. By contrast, T cells deficient for ketone body oxidation exhibit reduced mitochondrial function, increased exhaustion and fail to control tumour growth under DR conditions. Importantly, DR synergizes with anti-PD1 immunotherapy, further augmenting anti-tumour T cell responses and limiting tumour progression. Our findings reveal that T cell metabolic reprogramming is central to the anti-tumour effects of DR, highlighting nutritional control of CD8$^+$ T cell fate as a key driver of anti-tumour immunity.

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PREPRINT

Codon bias coevolves with longevity

Krisztina Kerekes, Mária Trexler, László Bányai, László Patthy

Somatic mutations drive carcinogenesis and aging, shortening the lifespan of animals. Since the vulnerability of genes strongly depends on their size and the abundance of mutation hotspots, we have tested whether negative selection of hypermutable (e.g., CpG bearing) codons could play a role in the evolution of longevity in mammals. Our studies have shown that the CGA codon was significantly more depleted in long-lived than short-lived mammals, suggesting negative selection of this hypermutable stopogenic codon. Interestingly, our analyses have revealed lifespan-dependent changes in codon usage of most amino acids. In the case of a few amino acids (e.g., Ile) the change in codon usage favored translationally optimal codons in long-lived animals, reducing the chances of mistranslation and the formation of abnormal proteins. In the case of a larger group of amino acids (e.g., Tyr, Phe, Asp, Asn), however, the change in codon usage in long-lived animals favored translationally nonoptimal codons that lack matching isodecoder tRNAs. The most likely explanation for this observation is that slowdown of translation at these codons facilitates co-translational folding, thereby reducing the chances of misfolding and aggregation of misfolded proteins in long-lived animals. Our results suggest that the changes in codon usage may contribute significantly to correct co-translational folding, resulting in a more balanced proteostasis and a lower rate of cellular aging in long-lived animals. Our finding is in harmony with the notion that one of the most important hallmarks of aging is loss of proteostasis, manifested in the accumulation of abnormal, misfolded proteins.

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PREPRINT

Parallel Selection for Longevity in Mammals and Birds

William B. Zhang, Marcus R. Kronforst

Most studies of aging biology to date have involved the manipulation of short-lived model organisms, while the existing anti-aging mechanisms in naturally occurring long-lived vertebrates have generally remained undiscovered or understudied. The technological advances of the recent "omics revolution" have enabled comparative genomics studies, which have started to unravel genetic signatures of longevity in vertebrates. Building on prior studies and incorporating a novel approach to detecting convergent positive selection, we conducted the first genome-wide survey of positive and purifying selection among hundreds of long-lived mammals and birds, two major vertebrate taxa with notable parallels in their evolutionary history. We discovered an extensive network of shared pathways under purifying selection in both mammals that are exceptionally long-lived for their body size (ELL) and large-bodied long-lived (LLL) birds. In our positive selection survey, we identified 16 genes, involved in eight distinct hallmarks of aging, with concordant signals of positive selection in LLL mammals and LLL birds at neighboring amino acid residues. These included two genes directly involved in cholesterol metabolism, as well as genes whose products clear oxidized metabolites and regulate peroxisomal autophagy. These striking parallels between long-lived mammals and birds, both in broad pathways under purifying selection, as well as in instances of genes under parallel positive selection in LLL mammals and LLL birds, together imply an ancient shared genetic toolkit for longevity, deeply conserved and repeatedly modified to produce longevity in diverse lineages.

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PREPRINT

Resilience to cardiac aging in Greenland shark *Somniosus microcephalus*

The Greenland shark (*Somniosus microcephalus*), with a lifespan exceeding 400 years, represents a unique model for studying vertebrate longevity. Here, we characterize its cardiac aging profile and compare it with two other species: the deep-sea shark *Etmopterus spinax* and the short-lived teleost *Nothobranchius furzeri*. Histological analysis revealed extensive interstitial and perivascular fibrosis throughout the ventricular myocardium of *S. microcephalus*, affecting both compact and spongy layers of both sexes. This fibrotic pattern was absent in *E. spinax* and *N. furzeri*, suggesting it is a specific feature of *S. microcephalus*. We also observed extreme lipofuscin accumulation within cardiomyocytes of *S. microcephalus*, which correlates at the ultrastructural level with abundance of damaged mitochondria and the presence of strikingly enlarged lysosomes filled with electrondense material of likely mitochondrial origin. Additionally, in the myocardium of *S. microcephalus* we found abundant deposition of the oxidative stress marker 3-nitrotyrosine. Remarkably, despite showing multiple canonical markers of aging such as fibrosis, lipofuscin accumulation, and oxidative damage, S. microcephalus individuals appeared healthy and physiologically uncompromised at the time of capture. These findings suggest that *S. microcephalus* has evolved resilience to molecular and tissue-level aging hallmarks, supporting sustained cardiac function over centuries and offering new insights into the mechanisms of extreme vertebrate longevity.

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Sterilization and contraception increase lifespan across vertebrates

Reproduction is hypothesized to constrain lifespan[1,2] and contribute to sex differences in ageing[3,4,5]. Various sterilization and contraception methods inhibit reproduction, but predictions differ for how these influence survival, depending on sex[5], how sex hormones are affected[4] and species life history[6]. Here, using data from mammalian species housed in zoos and aquariums worldwide, we show that ongoing hormonal contraception and permanent surgical sterilization are associated with increased life expectancy. These effects occur in both males and females, although the sexes are differently protected from specific causes of death. Evidence of improved survival in males is also restricted to castration, with stronger effects occurring after pre-pubertal surgery. Complementary meta-analyses of published data reveal improved survival with sterilization across vertebrates and increased healthspan in gonadectomized rodents. Improved survival occurs in laboratory and wild environments, and with female sterilization approaches that either remove the ovaries or leave them intact. Reported increases in survival in castrated men[7,8,9] resemble the effects in other species, whereas survival of women is slightly decreased after permanent surgical sterilization. Thus the hormonal drive to reproduce constrains adult survival across vertebrates, regardless of the environment in which an animal resides.

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Integration of multiple omics reveals key targets and cellular mechanisms for intervention in sarcopenia

Background: Sarcopenia, an age-related syndrome characterized by progressive loss of muscle mass, strength, and function, presents a significant global health burden with limited therapeutic interventions. This study integrates genomic causality, multi-tissue omics, and cellular mediation analyses to identify and prioritize mechanistically grounded therapeutic targets.

Methods: A multi-tiered analytical framework was applied, beginning with two-sample Mendelian randomization (MR) to infer causal relationships between 4907 plasma proteins (cis-pQTLs from 35,559 individuals) and sarcopenia traits in Pan-UK Biobank participants. Bayesian colocalization and transcriptomic validation in human sarcopenia muscle biopsies were employed to prioritize targets. Cellular mediation analysis quantified contributions of immune and stromal cell subtypes to protein-trait pathways using transcriptomic deconvolution.

Results: MR identified 1237 plasma proteins causally associated with sarcopenia traits, with six targets (HGFAC, GATM, HMOX2, F2, LMAN2L, HPGDS) validated through colocalization, transcriptomic expression, and sarcopenia-related dysregulation. Cellular mediation revealed immune mechanisms underlying HGFAC's effects, with CD4+ regulatory T cells mediating 3.49 % of its impact on sarcopenia traits. Prothrombin exhibited muscle-protective effects independent of coagulation.

Conclusion: This study establishes a causal map linking plasma proteins to sarcopenia through immune-stromal interactions. The integration of MR, multi-omics validation, and cellular mediation prioritizes six proteins as actionable targets, supporting repurposing of thrombin inhibitors and development of immunometabolic therapies. The framework bridges genomic causality with cellular pathophysiology, advancing precision strategies for age-related muscle decline.

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Transient hepatic reconstitution of trophic factors enhances aged immunity

Ageing erodes human immunity, in part by reshaping the T cell repertoire, leading to increased vulnerability to infection, malignancy and vaccine failure[1,2,3]. Attempts to rejuvenate immune function have yielded only modest results and are limited by toxicity or lack of clinical feasibility[1,3,4,5]. Here we show that the liver can be transiently repurposed to restore age-diminished immune cues and improve T cell function in aged mice. These immune cues were found by performing multi-omic mapping across central and peripheral niches in young and aged animals, leading to the identification of Notch and Fms-like tyrosine kinase 3 ligand (FLT3L) pathways, together with interleukin-7 (IL-7) signalling, as declining with age. Delivery of mRNAs encoding Delta-like ligand 1 (DLL1), FLT3L and IL-7 to hepatocytes expanded common lymphoid progenitors, boosted de novo thymopoiesis without affecting haematopoietic stem cell (HSC) composition, and replenished T cells while enhancing dendritic cell abundance and function. Treatment with these mRNAs improved peptide vaccine responses and restored antitumour immunity in aged mice by increasing tumour-specific $CD8^+$ infiltration and clonal diversity and synergizing with immune checkpoint blockade. These effects were reversible after dosing ceased and did not breach self-tolerance, in contrast to the inflammatory and autoimmune liabilities of recombinant cytokine treatments[6,7]. These findings underscore the promise of mRNA-based strategies for systemic immune modulation and highlight the potential of interventions aimed at preserving immune resilience in ageing populations.

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PREPRINT

Ensemble-DeepSets: an interpretable deep learning framework for single-cell resolution profiling of immunological aging

Immunological aging (immunosenescence) drives increased susceptibility to infections and reduced vaccine efficacy in elderly populations. Current bulk transcriptomic aging clocks mask critical cellular heterogeneity, limiting the mechanistic dissection of immunological aging. Here, we present Ensemble-DeepSets, an interpretable deep learning framework that operates directly on single-cell transcriptomic data from peripheral blood mononuclear cells (PBMCs) to predict immunological age at the donor level. Benchmarking against 27 diverse senescence scoring metrics and existing transcriptomic clocks across four independent healthy cohorts demonstrates superior accuracy and robustness, particularly in out-of-training-distribution age groups. The model's multi-scale interpretability uncovers both conserved and cohort-specific aging-related gene signatures. Crucially, we reveal divergent contributions of T cell subsets (pro-youth) versus B cells and myeloid compartments (pro-aging), and utilize single-cell resolution to highlight heterogeneous aging-associated transcriptional states within these functionally distinct subsets. Application to Systemic Lupus Erythematosus (SLE) reveals accelerated immune aging linked to myeloid activation and altered myeloid subset compositions, illustrating clinical relevance. This framework provides a versatile tool for precise quantification and mechanistic dissection of immunosenescence, providing insights critical for biomarker discovery and therapeutic targeting in aging and immune-mediated diseases.

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Comparative analysis of human and mouse ovaries across age

We performed a multimodal analysis of human and C57BL6/J mouse ovaries at young and advanced reproductive ages. We combined three-dimensional tissue imaging, single-cell RNA sequencing (scRNA-seq), and functional assays to define shared and species-specific features of oocyte follicle distribution, follicle growth and maturation, cellular composition and signaling, and age-associated changes.

High-resolution imaging of optically cleared intact mouse ovaries and human ovary fragments revealed discrete cortical "pockets" of human oocytes that shrink with age. Follicle density decreased with age in both species, and early decline of secondary-stage follicles in mice suggests vulnerability specific to stages of growth. scRNA-seq captured all major ovarian cell types and revealed both conserved and species-specific subtypes. Mature oocytes from both species shared enriched pathways, whereas immature oocytes diverged more substantially. Aging altered the transcriptome of oocytes in humans and mice more compared with that of surrounding granulosa cells, although early-stage oocytes were more changed in mice, and late-stage oocytes were more changed in humans.

Subtype analysis revealed that granulosa, fibroblast, and endothelial cells shared conserved transcriptional programs, whereas species-specific subtypes emerged in theca, pericyte, and epithelial compartments. Ovarian glial cells were identified in both species, frequently in association with sympathetic nerves. Innervation was implicated in the growth of follicles by genetically ablating sympathetic nerves in mice, and pericytes were shown as the major source of nerve growth factor. Networks of ovarian nerves became more dense with age in mouse and human samples. In ovarian fibroblasts, age-related transcriptional changes included down-regulation of collagen genes, despite increased deposition of collagen protein in aged human ovaries, suggesting a conserved compensatory mechanism for fibrosis.

Functionally, the competence and developmental potential of mouse oocytes declined markedly by 9 months of age, recapitulating the age dependence of human in vitro fertilization. Intercellular signaling between oocytes, granulosa, and theca cells was altered with age, revealing species-shared and -specific changes in pathways regulating oocyte support and maturation.

Vegetarian diet and likelihood of becoming centenarians in Chinese adults aged 80 y or older: a nested case–control study

Background: Inverse associations of vegetarian diet with morbidity and mortality have been observed; however, the role of vegetarian diet on exceptional longevity remains unrevealed.

Objectives: This study aims to examine the association between a vegetarian diet and likelihood of becoming a centenarian in adults aged ≥80 y.

Methods: This prospective nested case-control study included 5203 participants aged 80+ y from the Chinese Longitudinal Healthy Longevity Survey, a nationally representative cohort initiated in 1998. Participants were classified as omnivores and vegetarians, and further into vegetarian subgroups (pesco-vegetarians, ovo-lacto-vegetarians, and vegans) based on consumption of animal-derived foods. The primary outcome was living to 100 y old by the end of follow-up (2018). Multivariable unconditional logistic regression models were used to evaluate the association analysis.

Results: The study identified 1459 centenarians and matched them with 3744 noncentenarians (who had deceased before reaching 100 y). Relative to omnivores, vegetarians had a lower likelihood of becoming centenarians [odds ratio (OR): 0.81, 95% confidence interval (CI): 0.69, 0.96], and similar patterns were observed for vegans (OR: 0.71, 95% CI: 0.54, 0.98), but not for pesco-vegetarians (OR: 0.84, 95% CI: 0.64, 1.09) and ovo-lacto-vegetarians (OR: 0.86, 95% CI: 0.67, 1.09). The significant association was seen in individuals with BMI <18.5 kg/m^2 (OR: 0.72, 95% CI: 0.57, 0.91), but not for those with BMI ≥18.5 kg/m^2 (OR: 0.92, 95% CI: 0.73, 1.17) (P-interaction = 0.08).

Conclusions: Targeting individuals of advanced age (80+ y) in China, we found that individuals following a vegetarian diet had a lower likelihood of becoming centenarians relative to omnivores, underscoring the importance of a balanced, high-quality diet with animal- and plant-derived food composition for exceptional longevity, especially in the underweight oldest-old.

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Adherence to the 24-Hour Movement Guidelines is related to a lower risk of all-cause mortality: A prospective cohort study of 14,288 participants from the SUN Project

Objective: The purpose of this study is to examine the associations between adherence to the 24-Hour Movement Guidelines and all-cause and cause-specific mortality in a large Spanish prospective cohort.

Methods: We analyzed data from 14,288 participants of the Seguimiento Universidad de Navarra (SUN) Project, followed for a mean of 12.8 years (mean baseline age = 38.3 years; 60.1% women). Data were collected at baseline and through biennial follow-up questionnaires (up to 10 waves, depending on year of entry). The participants self-reported 24-h movement behaviors at baseline and were categorized based on the number of guidelines met (0-3). Behaviors were assessed at baseline only; changes in adherence during follow-up were not accounted for. Cox proportional hazards models were used to estimate hazard ratios (HRs) for all-cause and cause-specific mortality, adjusting for sociodemographic, lifestyle, and clinical covariates.

Results: Meeting a greater number of 24-Hour Movement Guidelines at baseline was associated with a progressively lower risk of all-cause mortality. Compared with those meeting none, the multivariable-adjusted HRs were 0.52 (95% confidence interval (95%CI): 0.33-0.82) for meeting one guideline, 0.47 (95%CI: 0.30-0.73) for meeting two guidelines, and 0.44 (95%CI: 0.28-0.71) for meeting all three guidelines. Only adherence to the physical activity guidelines was independently associated with a significantly lower mortality risk (HR = 0.70; 95%CI: 0.55-0.89). A reduced risk was also observed for cancer and other-cause mortality among those meeting two or more guidelines.

Conclusion: Adherence to the 24-Hour Movement Guidelines at baseline, particularly physical activity, was associated with a lower risk of mortality. Promoting an integrated approach to movement behaviors may be an effective strategy for improving population health and longevity.

Intrinsic capacity–frailty phenotypes and subclinical inflammation in community-dwelling octogenarians: A cross-sectional analysis from the ilSIRENTE study

Methods

IC was assessed across five domains (locomotion, cognition, vitality, psychological well-being, and sensory function), rescaled to a 0–100 range, and combined with frailty status to define four IC–frailty phenotypes (concordant frail, discordant low IC, discordant high IC, concordant robust). Plasma C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) were measured, and a composite inflammatory burden score (0–3) was derived.

Results

The analysis included 311 participants (mean age 85.4±4.7 years, 66.6% women). Median CRP, IL-6, and TNF-α levels increased progressively from concordant robust to concordant frail groups ($p<0.01$). In the fully adjusted model, concordant frail participants had higher inflammation compared with concordant robust (β=0.71; 95% CI 0.04–1.37; $p=0.03$), while discordant high IC and discordant low IC showed intermediate values without statistical significance. A significant linear trend was observed across ordered phenotypes (β per category increment=0.21, 95% CI 0.06 to 0.37). Locomotion and vitality emerged as the domains most strongly linked to inflammation.

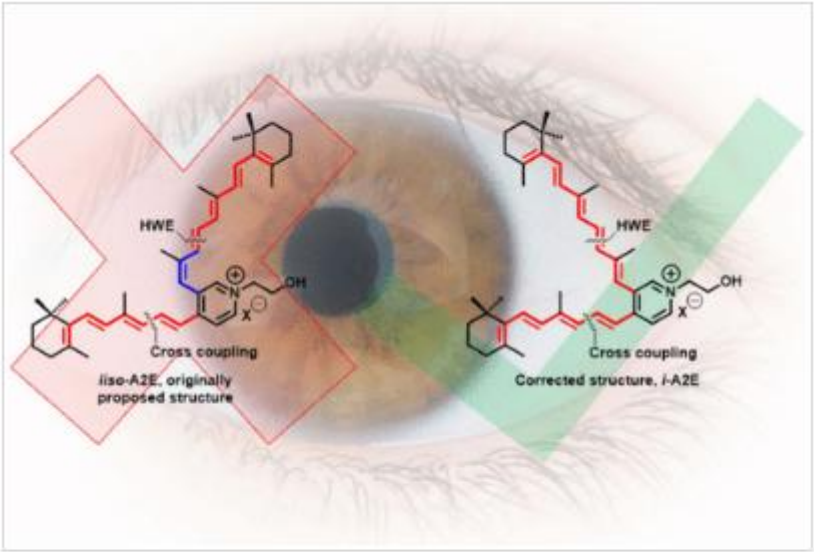
Conclusions

IC–frailty phenotypes show a biological gradient of subclinical inflammation, with higher IC having lower inflammation levels. Preserved locomotion reflects key functional correlates of resilience and vitality in advanced age.

Stereochemical Reassignment by Total Synthesis of an Ocular Pyridinium Bisretinoid of Retinal Pigment Epithelium Lipofuscin: *iiso*-A2E Is *i*-A2E

Brais Vidal, Oscar Iglesias-Menduiña, Belén Vaz, Rosana Álvarez*, Claudio Martínez*, and Ángel R. de Lera*

The stereoselective synthesis of recently discovered lipofuscin fluorophore *iiso*-A2E, a C3,C4-bis-polyenylpyridinium salt derived from all-*trans*-retinal, which has been detected in human, pig, mouse, and bovine eyes, has been completed. The Suzuki–Miyaura cross-coupling reaction and Horner–Wadsworth–Emmons condensation were the key synthetic steps for the construction of the tetraenyl and pentaenyl arms, respectively, starting from a properly functionalized pyridine-3,4-dialdehyde surrogate, followed by pyridine alkylation. Subtle changes in the ^{1}H NMR and ^{13}C NMR spectra of the synthetic compound and natural compound suggested the structural revision of the latter, for which the C13'=C14' *E* isomer at the longer C3-unsaturated pentaenyl chain of the pyridinium ring was proposed. The synthesis confirmed the alternative stereostructure of the natural pigment, which should be named *i*-A2E, thus correcting the double bond geometry of the natural fluorophore at C13'=C14'.



C. elegans aging research

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PREPRINT

Multiple Molecular Pathways to Longevity: Opposing Gene Expression Programs Define Distinct Aging Strategies

While aging is the greatest risk factor for the development of neurodegenerative disease, the role of aging in these diseases is poorly understood. Our previous work has shown that targeting aging pathways can be neuroprotective in animal models of neurodegenerative disease. Based on these findings, we believe that by gaining insight into the aging process, that knowledge can be applied to identify novel therapeutic targets for neurodegenerative disease. To advance our understanding of aging, we used a genomics approach to identify genes regulated by multiple lifespan-extending pathways. We performed RNA sequencing on nine long-lived *C. elegans* mutants representing seven longevity pathways: insulin/IGF-1 signaling, dietary restriction, germline deficiency, impaired chemosensation, reduced translation, elevated mitochondrial ROS, and mild mitochondrial impairment. We found that most pairs of long-lived mutants exhibited a significant overlap in differentially expressed genes. Comparing gene expression across the entire panel of long-lived mutants revealed three distinct longevity groups that could be clearly distinguished by gene expression. Interestingly, two of these groups showed modulation of specific genetic pathways in opposite directions, suggesting that there are multiple alternative strategies to achieving long life. Filtering for genes similarly modulated in at least six mutants identified 196 upregulated and 62 downregulated aging genes. Upregulated genes were enriched in immunity, defense and metabolism, while many downregulated genes impacted translation and gene expression. To assess the ability of these genes to enhance longevity individually, we knocked down the commonly upregulated genes in long-lived mutants and evaluated the resulting effect on lifespan. Using this approach, we identified several genes that affect lifespan individually. Upregulation of at least some of these genes was sufficient to enhance stress resistance and extend lifespan in wild-type worms. Overall, the shared longevity genes identified in this work offer potential targets to promote healthy aging and decrease age-onset disease.

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PREPRINT

A Fourfold Male-Specific Lifespan Extension via Canonical Insulin/IGF-1 Signaling

The insulin/IGF-1 signaling (IIS) pathway is an evolutionary conserved regulator of longevity, and its modulation is a hallmark of aging research. The 1993 ground-breaking report of a *daf-2* mutation (e1370) that reduced IIS and doubled *C. elegans* lifespan in hermaphrodite worms paved the way for molecular approaches to modulating aging. However, the impact of that mutation on the male sex has remained largely unstudied. Here we report that the same mutation extends male lifespan by fourfold, to over 110 days. This extreme longevity is coupled with a dramatic extension of healthspan as well. These findings establish sex not as a secondary variable but as a primary determinant of longevity potential, capable of amplifying the output of a core aging pathway to an astonishing degree. This work provides a new approach or dissecting the interplay between sex and aging and suggests that sex-specific interventions may be critical for developing future anti-aging therapeutics.

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PREPRINT

Lifespan-extending downregulation of insulin signalling reduces germline mutation load

Reduced insulin/IGF-1 signalling (IIS) robustly extends lifespan and enhances somatic stress resistance across taxa, yet its consequences for germline genome integrity remain unclear. Here we combine multigenerational mutation accumulation with whole-genome sequencing in *C. elegans* to test whether adulthood-only IIS downregulation can simultaneously promote somatic maintenance and limit germline mutational burden. We reduced IIS by adult-onset *daf-2* RNAi in wild-type and heritable RNAi-deficient (*hrde-1*) backgrounds, allowing either spontaneous or UV-induced germline mutations to accumulate over multiple generations. In wild-type animals, reduced IIS lowered germline single-nucleotide mutation rates by up to ~50% and prevented the UV-induced elevation in mutation rate, without detectable costs to fecundity or lineage persistence. By contrast, in *hrde-1* mutants the same intervention increased both point mutations and transposable-element–driven insertions under UV exposure, accelerating lineage extinction. Thus, the genome-protective effect of reduced IIS critically requires the germline nuclear Argonaute HRDE-1, which mediates small-RNA–guided epigenetic silencing. Functional annotation of germline variants revealed enrichment in pathways linked to development, cellular maintenance and conserved longevity regulators, including IIS and mTOR, and identified high-impact mutations in genes with human orthologs implicated in neurodegeneration and cancer. Our findings show that IIS can coordinate somatic and germline maintenance in concert, rather than in competition, through an HRDE-1–dependent epigenetic pathway. This work positions nutrient-sensing IIS as a central regulator of germline genome stability and suggests that IIS downregulation can reduce germline mutation load while extending lifespan, with broad implications for biogerontology and evolutionary biology.

REVIEWS/COMMENTS/ METHODS/EDITORIALS

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EDITORIAL

Editorial > Expert Opin Pharmacother. 2025 Dec 19:1-3. doi: 10.1080/14656566.2025.2605205.
Online ahead of print.

Advanced antiaging therapies: what can we expect for 2026?

Ricardo P Garay [1] [2]

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PERSPECTIVE

Do we actually need aging clocks?

Dmitrii Kriukov, Evgeniy Efimov, Mikhail S. Gelfand, Alexey Moskalev & Ekaterina E. Khrameeva

Aging clocks use machine learning to estimate biological age as a proxy for general health state. Here, we critically examine their practical value, highlighting fundamental challenges: abstract definitions, inconsistent clinical validation, and ignored prediction uncertainty. By comparing aging clocks with expert risk scores, direct outcome predictors, and emerging large health models, we question their benefits and encourage researchers to explicitly justify clock advantage over established alternatives, ensuring truly actionable insights.

Hematopoietic (stem) cells—The elixir of life?

The long lifespan of humans is often not matched with health span. Thus, there is a need for rejuvenation strategies. Here, we first discuss the evolutionary benefits of the long human lifespan, particularly when coupled with an extended health span. We then highlight the importance of understanding the complexity of aging before interfering with it. This raises the question of the optimal target for rejuvenation. We propose the blood system and hematopoietic stem cells (HSCs). Their decline is associated with dysfunction and disease in other organs, crystallizing them as a central player in organismal aging. We present rejuvenation strategies targeting the hematopoietic system, especially HSCs, and explore their systemic benefits. Overall, we summarize the potential of the blood system to reverse aging.

Sympathetic-parasympathetic system deregulation theory of aging

The central nervous system, comprised of the brain, spinal cord, and nerves, includes the autonomic nervous system (ANS) that regulates involuntary functions. Within the ANS, the sympathetic and the parasympathetic nervous systems (SNS and PNS, respectively) control the same bodily functions, but in opposing directions. For example, the sympathetic nervous system elicits our "fight or flight" response, while the parasympathetic system supports "rest and repair" mechanisms in the broadest possible sense. With age, changes occur in how information is transmitted, in energetic requirements and expenditures, and in the ability to respond to change. These alterations with age result in the "hallmarks of aging", specifically including genomic instability, telomere attrition, epigenetic changes, loss of proteostasis, deregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and chronic inflammation. Understanding these age-dependent changes is essential for promoting healthy aging and longevity. We propose that, at the core of aging, there is an imbalance between the SNS and PNS, which provides opportunities for therapeutic intervention.

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Pineal gland senescence: an emerging ageing-related pathology?

An ageing-related pathology has recently been described as one that develops and/or progresses with increasing chronological age, that is associated with, or contributes to, functional decline and that is evidenced by studies in humans. The pineal gland is a photo-neuroendocrine organ whose primary function is to produce and secrete melatonin in response to light-dark cycle environmental cues. The gland may undergo ageing-related structural and morphological changes, including calcification, gliosis, cyst formation, and reduced density of β-adrenergic receptors, which are hypothesised to reduce melatonin secretion. Pineal gland senescence describes the ageing-related decline in neuroendocrine function, with reduced secretion of melatonin, which may contribute to ageing-related sleep disorders and disruption of other circadian-driven physiological functions and may have secondary effects such as contributing to cognitive and mood disorders related to sleep disturbance.

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Genomic Perspective on Heterogeneity of Organs and Body Aging

Aging is a heterogeneous process, with organ systems and individuals experiencing variable rates of decline that are not fully reflected by chronological age. This variability contributes to the complexity of system morbidity, which poses increasing challenges for clinical care and biomedical research. In this review, we discuss the heterogeneity of organ and whole-body aging and perspectives on genomics as possible mechanisms that relate to such heterogeneity. We discuss how static genomics, including nuclear genetic variants, and dynamic genetics, such as somatic mutations, epigenetic drifts, and mitochondrial DNA changes might explain the variable rate of aging across organ systems and the whole body. We discuss that the use of metrics that capture heterogeneity in organ and body aging is critical to identify genomic biomarkers of aging, clarifying mechanisms of adaptation versus decline.

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Aging as a multifactorial disorder with two stages

David Gems [1], Alexander Carver [1], Yuan Zhao [2]

Aging (senescence) is characterized by development of diverse senescent pathologies and diseases, leading eventually to death. The major diseases of aging, including cardiovascular disease, cancer and chronic obstructive pulmonary disease (COPD), are multifactorial disorders, resulting from complex interactions between multiple etiologies. Here we propose a general account of how different determinants of aging can interact to generate late-life disease. This account, initially drawn from studies of the nematode *Caenorhabditis elegans*, depicts senescence as the product of a two-stage process. The first stage involves the diverse causes of disease prior to aging, that cause disruption of normal biological function. These include infection, mechanical injury and mutation (somatic and inherited). Second, etiologies largely confined to aging: deleterious, late-life consequences of evolved wild-type gene action, including antagonistic pleiotropy. Prior to aging, diverse insults lead to accumulation of various forms of injury that is largely contained, preventing progression to major pathology. In later life, wild-type gene action causes loss of containment of latent disruptions, which form foci for pathology development. Pathologies discussed here include osteoarthritis, cancer, late-life recrudescence of infection, and consequences of late-acting deleterious mutations. Such latent injury foci are analogous to seeds which in later life, in the context of programmatic senescent changes, germinate and develop into disease.

Changing the paradigm: The biggest polluter and threat to your health is your body

Edward J Calabrese [1]

This Commentary challenges the longstanding paradigm that the vast majority of cancers and many other serious aging-related diseases are principally due to environmental contamination. In contrast, it is argued that the major cause of aging-related diseases is the massive generation of oxy radicals produced by normal metabolic processes which, over time, initiate and promote the vast spectrum of aging-related diseases. This perspective leads to the conclusion that our bodies pose our biggest public health and medical threats. Failure to identify the major targets of aging-related diseases by environmental and public health agencies has resulted in incorrect priorities, the wasteful misdirection of funding, and the failure to improve the public health.

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mTOR signaling networks: mechanistic insights and translational frontiers in disease therapeutics

Hanxiao Zhang [1], Xia Xiao [1], Zhenrui Pan [1 2], Svetlana Dokudovskaya [3]

The mammalian target of rapamycin (mTOR) pathway is a central regulator of cellular growth, metabolism, and homeostasis, integrating a wide array of intracellular and extracellular cues, including nutrient availability, growth factors, and cellular stress, to coordinate anabolic and catabolic processes such as protein, lipid, and nucleotide synthesis; autophagy; and proteasomal degradation. The dysregulation of this signaling hub has broad implications for health and disease. To commemorate the 50th anniversary of the discovery of rapamycin, we provide a comprehensive synthesis of five decades of mTOR research. This review traces the historical trajectory from the early characterization of the biological effects of rapamycin to the elucidation of its molecular target and downstream pathways. We integrate fundamental and emerging insights into the roles of mTOR across nearly all domains of cell biology and development, with a particular focus on the expanding landscape of therapeutic interventions targeting this pathway. Special emphasis is placed on the crosstalk between mTOR signaling and mitochondrial regulation, highlighting the mechanisms by which these two metabolic hubs co-regulate cellular adaptation, survival, and disease progression. The dynamic interplay between mTOR and mitochondrial networks governs key aspects of bioenergetics, redox balance, and cell fate decisions and is increasingly implicated in pathophysiological contexts ranging from cancer and aging to neurodegenerative and immune disorders.

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Antisense Oligonucleotide Therapeutics Targeting Age-Related Diseases

The rapid growth in the global aging population has intensified concerns regarding age-related diseases (ARDs), which pose substantial health and socioeconomic burdens. Current therapeutic strategies, such as small-molecule drugs, primarily target downstream pathophysiological manifestations, including inflammation, fibrosis, and metabolic imbalance, but have limited ability to address the underlying molecular causes of disease. Antisense oligonucleotides (ASOs) are emerging as a promising modality capable of precise, sequence-specific regulation of gene expression at the RNA level, offering the potential to directly modulate disease etiology. This review examines the relationship between major ARD categories and the hallmarks of aging and highlights recent research trends in ASO-based therapeutics. We explore the connections between hallmark aging processes and major ARDs, including neurodegenerative, cardiovascular, metabolic, and musculoskeletal disorders, emphasizing dysregulated genes that contribute to disease progression. Preclinical and clinical studies demonstrate that ASOs can offer targeted intervention against key pathological mechanisms such as protein aggregation, chronic inflammation, metabolic dysfunction, and tissue fibrosis by modulating gene expression. Despite their promise, major challenges remain, including poor tissue-specific delivery, limited penetration into certain tissues, and concerns around long-term safety. Emerging delivery strategies such as ligand conjugates and lipid nanoparticle systems are expanding the therapeutic reach of ASOs. By providing a programmable approach to precisely regulate pathogenic gene expression, ASOs have the potential to redefine the therapeutic landscape for ARDs in an aging society. This review provides an integrated perspective on these advances and their implications for future therapeutic development.

Exploring Splicing–Energy Axis Associations to Diet and Longevity

Stefano Donega [1], Myriam Gorospe [2], Luigi Ferrucci [1]

There is increasing evidence that nutrient composition, even without lowering total calorie intake, can shape lifespan through mechanisms independent of mitochondrial regulation. Brandon and colleagues recently reported that a low-protein, high-carbohydrate (LPHC) diet enriched with non-digestible cellulose, extends lifespan in mice by shifting the liver proteome through altered RNA splicing, a response different from the mitochondrial improvements typically seen with caloric restriction. The authors' findings support the "energy-splicing resilience axis," which proposes that changes in splicing help cells adapt to energetic and nutritional stress. We discuss how diet influences spliceosomal components such as SRSF1, linking nutrient sensing, AMPK signaling, and tissue-specific resilience pathways. We also consider the splicing paradox in aging, where beneficial isoforms increase despite a concomitant increase in splicing errors. Understanding how dietary and pharmacologic interventions modulate splicing may shed light on strategies to maintain homeostatic proteomes and support healthy longevity.

Toward precision longevity: aging interventions in the single-cell atlas era

With growing global interest in extending not only lifespan but also healthspan, healthy aging has emerged as a central goal in biomedical research. This review provides an overview of current longevity interventions, including genetic manipulations, dietary restriction, exercise, pharmacological treatments, targeting senescence and cellular reprogramming strategies, as studied in key model organisms such as *Caenorhabditis elegans*, *Drosophila melanogaster*, and *Mus musculus*. We examine the limitations and challenges associated with these approaches, particularly their variability across tissues and cell types. Furthermore, we emphasize the critical role of single-cell aging atlas technologies in uncovering cell-type-specific aging patterns and molecular signatures. By integrating single-cell data, we propose that future interventions can be more precisely designed to target aging at the cellular level, thereby enhancing the efficacy and specificity of longevity strategies.

Cell-based immunotherapy for neurodegenerative disease: A promising avenue

Neurodegenerative diseases such as amyotrophic lateral sclerosis, Alzheimer's disease, Parkinson's disease, and Huntington's disease are characterized by progressive neuronal loss and chronic neuroinflammation, with current treatments remaining largely symptomatic. This review explores the potential of cell-based immunotherapy as a disease-modifying strategy. Advances in stem cell biology and immune engineering have facilitated the development of therapies using mesenchymal stem cells, chimeric antigen receptor T cells, macrophages, regulatory T cells, modified macrophages, and monoclonal antibodies. These approaches aim to regulate immune mechanisms implicated in neurodegeneration, such as microglial activation, systemic inflammation, and immune checkpoint dysregulation. Notably, macrophage-mediated delivery systems, such as genetically modified cells expressing neurotrophic factors or antioxidant enzymes, have demonstrated neuroprotective effects. Likewise, emerging data support T-cell modulation and monoclonal antibody development as therapeutic targets in amyotrophic lateral sclerosis, Alzheimer's disease, Parkinson's disease, and Huntington's disease. We highlight current preclinical findings, underlying mechanisms, and translational challenges, emphasizing that immunomodulatory cell therapies represent a promising avenue for precision medicine in neurodegenerative diseases.

Longevity, Centenarians, and Lifestyle: Any ''Tips'' to Live Longer?

In this narrative review, we provide an overview of the current understanding of the lifestyle factors that are associated with longevity and healthy aging, having Centenarians as a reference population. RECENT FINDINGS: Despite cultural differences, Centenarians exhibit common behavioural patterns and lifestyle habits believed to promote longevity. In particular, plant-based dietary patterns provide antioxidant and anti-inflammatory properties, thus counteracting physiological and pathophysiological processes relating to unsuccessful aging. Regular physical activity reduces inflammation and preserves lean mass, leading to metabolic fitness and adequate body composition. Finally, meditation practices have been shown to reduce stress reactivity and inflammatory responses related to cortisol secretion. This multifactorial approach might improve the health status and life quality of older people as a priority of the continuous increase of the ageing population. For the promotion of successful aging, lifestyle interventions should follow a multifactorial approach. This review offers specific recommendations to promote longevity in the general population, including plant-based eating patterns, physical activity and psychological well-being.

Epigenetic Clocks in Skin Aging: From Exposome Drivers to Biomarkers and Therapeutic Interventions

Skin aging is a multifactorial process driven by a combination of intrinsic genetic programming and extrinsic environmental exposures. Recent advances in epigenetics have illuminated how changes in DNA methylation, histone modifications, and non-coding RNAs regulate skin aging, with the epigenetic clock emerging as a powerful tool to quantify biological age. This review aims to synthesize current evidence on how environmental and lifestyle factors - particularly ultraviolet radiation, pollution, smoking, diet, and stress - accelerate skin aging through epigenetic mechanisms, while also evaluating the potential of skin-specific epigenetic clocks as biomarkers for early detection of premature aging and for guiding therapeutic interventions. We further discuss the expanding field of epigenetic-targeted therapies in dermatology, encompassing topical agents, energy-based devices, and systemic approaches that may reverse or delay visible signs of cutaneous aging. By integrating insights from molecular biology, environmental science, and clinical dermatology, this review positions skin aging not as an irreversible outcome but as a modifiable, biologically regulated process with promising avenues for personalized prevention and rejuvenation.

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From Elixirs to Geroscience: A Historical and Molecular Perspective on Anti-Aging Medicine

Giuseppe Rosario Pietro Nicoletti [1], Katia Mangano [1], Ferdinando Nicoletti [1], Eugenio Cavalli [1]

The pursuit of youth and longevity has accompanied human societies for millennia, evolving from mythological and esoteric traditions toward a scientific understanding of aging. Early concepts such as Greek ambrosia, Taoist elixirs, and medieval "aqua vitae" reflected symbolic or spiritual interpretations. A major conceptual transition occurred between the late nineteenth and early twentieth centuries, when aging began to be framed as a biological process. Pioneering ideas by Metchnikoff, together with early and sometimes controversial attempts such as Voronoff's grafting experiments, marked the first efforts to rationalize aging scientifically. In the mid-twentieth century, discoveries including the Hayflick limit, telomere biology, oxidative stress, and mitochondrial dysfunction established gerontology as an experimental discipline. Contemporary geroscience integrates these insights into a coherent framework linking cellular pathways to chronic disease risk. Central roles are played by nutrient-sensing networks such as mTOR, AMPK, and sirtuins, together with mitochondrial regulation, proteostasis, and cellular senescence. Interventions, including caloric restriction, fasting-mimicking diets, rapalogues, sirtuin activators, metformin, NAD^+ boosters, senolytics, and antioxidant combinations such as GlyNAC, show consistent benefits across multiple model organisms, with early human trials reporting improvements in immune function, mitochondrial activity, and biomarkers of aging. Recent advances extend to epigenetic clocks, multi-omic profiling, gender-specific responses, and emerging regenerative and gene-based approaches. Overall, the evolution from historical elixirs to molecular geroscience highlights a shift toward targeting aging itself as a modifiable biological process and outlines a growing translational landscape aimed at extending healthspan and reducing age-related morbidity.

Associations between phosphodiesterase type 5 inhibitors and vascular function: a systematic review and meta-analysis on randomized-controlled trials

Background: Phosphodiesterase type-5 inhibitors (PDE5is) are used for the treatment of erectile dysfunction (ED) and have potential cardioprotective effects. The impacts of PDE5is on cardiovascular parameters, which may be associated with the occurrence and progression of subclinical cardiovascular diseases, remain uncertain. In this study, we evaluated the effects of PDE5is on vascular parameters.

Methods: Randomized controlled trials (RCTs) that compared the effects of PDE5is and placebo on vascular parameters and were published from 1998 to 2022 were identified from PubMed, Scopus and Web of Science. Mean differences (MDs) with 95% confidence intervals (CIs) were pooled. A sensitivity analysis was conducted to confirm the robustness of the pooled results. The keywords that were searched in the databases are as follows: ((systolic blood pressure) OR (SBP) OR (diastolic blood pressure) OR (DBP) OR (mean arterial pressure) OR (MAP) OR (Pulse Wave Velocity) OR (PWV) OR (intima-media thickness) OR (cIMT) OR (augmentation Index) OR (AI) OR (FMD) OR (flow-mediated dilation) OR (reactive hyperemia index) OR (RHI) OR (Endothelial microparticles) OR (EMP) OR (EPCs) OR (Endothelial Progenitor Cells) OR (PSV) OR (peak systolic velocity)) AND ((PDE5 Inhibitors) OR (PDE5i) OR (Sildenafil) OR (Vardenafil) OR (Tadalafil) OR (Lodenafil) OR (Udenafil) OR (Avanafil)).

Results: Sixty-three studies involving 3242 subjects were included. Overall, PDE5is decreased systolic blood pressure (MD: -2.80 mmHg, 95% CI: -4.24, -1.37, $P < 0.001$), diastolic blood pressure (MD: -1.80 mmHg, 95% CI: -2.37, -1.22, $P < 0.001$), carotid intima–media thickness (MD: -0.01 mm, 95% CI: -0.02, -0.01, $P < 0.001$), and pulse wave velocity (MD: -0.75 cm/s, 95% CI: -1.01, -0.49, $P < 0.001$). In addition, PDE5is increased the peak systolic velocity (MD: 3.70 cm/s, 95% CI: 3.52, 3.88, $P < 0.001$), flow-mediated dilation (MD: 2.47%, 95% CI: 1.24, 3.71, $P < 0.001$), concentration of endothelial progenitor cells (MD: 475.29 cells/mL, 95% CI: 51.38, 899.20, $P = 0.03$), and concentration of endothelial microparticles (MD: 4.86%, 95% CI: 0.65, 9.07, $P = 0.02$). However, the effects of PDE5is on the augmentation index, brachial artery diameter and reactive hyperemia index were not statistically significant.

Conclusion: Compared with the placebo, PDE5is improved vascular parameters, indicating the potential of PDE5is for treating subclinical cardiovascular diseases. Further research is needed to confirm the role of the improvement on vascular parameters by PDE5isin preventing and treating cardiovascular diseases.

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Promising Results With NAD Supplementation in Rare Diseases With Premature Aging and DNA Damage

Nicotinamide adenine dinucleotide (NAD) has garnered significant attention in recent years due to its central role in cellular metabolism and its potential as a supplement to promote health and longevity. While numerous human studies indicate that NAD supplementation offers benefits with minimal or no side effects, some studies show no observable advantages. This discrepancy highlights the importance of identifying individuals who are most likely to benefit from NAD-based interventions. One critical factor in the efficacy of NAD supplementation relates to its declining levels in certain individuals, driven by various causes of NAD depletion. NAD is a vital substrate for numerous enzymatic processes, notably those involving poly-ADP-ribose polymerase (PARP) enzymes. PARP enzymes, especially PARP1, play a pivotal role in DNA repair by detecting and signaling DNA damage. Excessive activation of PARP, hyperparylation, is frequently observed in DNA repair disorders where DNA damage accumulates due to defective repair mechanisms. This hyperparylation has been implicated in the pathogenesis of several premature aging diseases. Such conditions often involve defective DNA repair pathways, elevated parylation levels, and associated mitochondrial dysfunction, factors that contribute to accelerated cellular aging. In model systems that mimic these disorders, as well as in emerging human studies, NAD supplementation has demonstrated promising benefits, including improved DNA repair capacity and improved mitochondrial function. These findings suggest that NAD supplementation could serve as an effective intervention for rare genetic diseases characterized by premature aging and DNA repair deficiencies. More broadly, these insights open new avenues for general aging research.

Wnt signaling pathway in lung aging and aging-related chronic lung diseases

As a target organ in direct contact with external air, lung tissue is more susceptible to aging, and lung aging is closely related to the development of chronic lung diseases such as chronic obstructive pulmonary disease and pulmonary fibrosis. Evolutionarily speaking, the Wnt signaling pathway is highly conserved and plays an important role in embryonic development, tissue homeostasis, as well as cell proliferation, differentiation, apoptosis, and migration of a variety of cells. Alterations in Wnt signaling pathway activity can accelerate the pathological process of chronic lung diseases. In recent years, a large number of studies have focused on the regulatory role of the Wnt signaling pathway in the lung aging process and aging-related chronic lung diseases. Therefore, this paper systematically reviews the relationship between the Wnt signaling pathway and lung aging and its role in aging-related chronic lung diseases.

Trained immunity in myocardial infarction: From mechanisms to translational potential

Myocardial infarction (MI) ranks among the leading causes of death globally, with its prognosis closely linked to inflammatory responses. Both excessive early inflammation and persistent residual inflammation lead to adverse cardiac remodeling and heart failure. In recent years, the role of trained immunity in cardiovascular risk factors and MI-associated inflammatory responses has garnered increasing attention. Cardiovascular risk factors can induce trained immunity, placing the body in a "preactivated" innate immune state prior to MI occurrence. This state is further amplified upon myocardial necrosis, triggering excessive inflammation. Additionally, MI itself can induce trained immunity, leading to long-term inflammatory memory and residual inflammation risk. Targeting metabolic and epigenetic pathways of trained immunity offers approaches for post-MI anti-inflammatory interventions. A comprehensive understanding of trained immunity's mechanisms in MI holds promise for establishing theoretical foundations and translational directions for precision anti-inflammatory therapies and improving long-term patient outcomes.

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Fluid biomarkers for neurodegenerative diseases: a comprehensive update

Fluid biomarkers are revolutionizing the diagnosis and management of neurodegenerative diseases by enabling earlier diagnosis and disease monitoring. In particular, blood-based biomarkers have emerged as a minimally invasive and scalable alternative to cerebrospinal fluid analysis. Recent advances in blood-based tau biomarkers have shown high diagnostic accuracy for Alzheimer's disease (AD). Other neurodegenerative diseases—such as synucleinopathies, frontotemporal lobar degeneration, limbic-predominant age-related TDP-43 encephalopathy (LATE), and amyotrophic lateral sclerosis—pose substantial challenges due to their heterogeneous clinical presentations and the current absence of robust biomarkers for hallmark pathologies. Nonetheless, promising candidate markers are emerging for improved disease characterization and staging. Technological innovations, including single-molecule arrays (Simoa), advanced mass spectrometry workflows and nucleic acid linked immune-sandwich assay (NULISA) have markedly enhanced the sensitivity and precision of biomarker quantification from low-concentration biological matrices. More recently, the development of fully automated platforms shows great promise for routine measurement of blood-based biomarkers in clinical settings. Despite this progress key challenges remain, including the need for improved assay reproducibility, standardization, and the optimization of clinical workflows. In this review, we provide a comprehensive update on recent progress in fluid biomarker research across AD and major neurodegenerative diseases, highlight technological advances in detection methods, and discuss current challenges and opportunities for clinical translation.

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Diapause and aging: Two opposing yet intertwined biological phenomena

Diapause is an evolutionarily conserved strategy that enables many organisms to survive prolonged exposure to harsh environmental stressors. During this state, organisms drastically reduce their metabolic rate, halt development, and enhance stress tolerance in an energy-efficient manner. Remarkably, many diapausing organisms appear to substantially slow or suspend aging as a result of profound metabolic depression and developmental arrest. Consequently, diapause and aging appear to be programmed in opposite directions, yet both rely on many of the same master regulatory genes and epigenetic modulators. This review explores the molecular mechanisms underlying diapause-induced stress resistance and metabolic suppression, offering critical insights into how dormant biological systems preserve function and delay aging. Manipulating these shared regulatory networks has led to significant extensions in lifespan and improvements in healthspan across various model organisms. Anhydrobiotic species such as Artemia, Caenorhabditis elegans, and tardigrades can nearly suspend aging during dormancy by downregulating metabolic pathways and accumulating protective macromolecules. Notably, the African turquoise killifish, which has adapted to life in ephemeral ponds, can provide a unique platform to study both diapause and aging within a single vertebrate model. Phenotypic plasticity may offer the most compelling evolutionary explanation for resolving the paradox of how the same regulatory network can produce opposite outcomes in diapause and aging. Overall, diapause offers a powerful natural framework for uncovering anti-aging mechanisms and holds great promise for guiding the development of novel interventions to promote longevity and healthy aging.

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Mesenchymal stem cells and their promise in reversing ovarian aging

Ovarian aging is accompanied by a decline in the quantity and quality of follicles, leading to reduced fertility. Ovarian aging encompasses natural aging due to DNA damage, telomere attrition, and mitochondrial dysfunction, as well as a pathological functional failure caused by environmental toxins, known as a premature ovarian failure. Cell therapy is currently a focal point of research, with mesenchymal stem cells (MSCs) being particularly notable due to their wide availability, ease of expansion, strong self-renewal capabilities, multipotent differentiation, and paracrine functions. MSCs have shown great potential in the field of cell therapy, including delaying ovarian aging. MSCs can delay ovarian aging through various mechanisms: antioxidation, differentiation and regeneration, promotion of cell proliferation, inhibition of cell apoptosis, and anti-inflammatory responses. Currently, MSCs transplantation has achieved significant results in animal models, improving ovarian function and enhancing fertility. However, clinical applications still face numerous challenges, such as determining the optimal cell source, transplantation route, dosage, and long-term safety, which require further research. In this review, we will elaborate on the mechanisms of ovarian aging, the modes of action of MSCs, and the mechanisms by which MSCs delay ovarian aging, aiming to provide a theoretical basis for the clinical application of MSCs and to bring breakthroughs in the treatment of diseases such as premature ovarian failure.

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Lipofuscin accumulation in aging and neurodegeneration: a potential "timebomb" overlooked in Alzheimer's disease

Lipofuscin, a marker of aging, is the accumulation of autofluorescent granules within microglia and postmitotic cells such as neurons. Lipofuscin has traditionally been regarded as an inert byproduct of cellular degradation. However, recent findings suggest that lipofuscin may play a role in modulating age-related neurodegenerative processes, and several questions remain unanswered. For instance, why do lipofuscin granules accumulate preferentially in aged neurons and microglia? What happens to these pigments upon neuronal demise? Particularly in neurodegenerative diseases like Alzheimer's disease (AD), why does amyloid β (Aβ) deposition usually begin in late adulthood or during aging? Why do lipofuscin and amyloid plaques appear preferentially in grey matter and rarely in white matter? In this review, we argue that lipofuscin should be revisited not as a simple biomarker of aging, but as a potential modulator of neurodegenerative diseases. We synthesize emerging evidence linking lipofuscin to lysosomal dysfunction, oxidative stress, lipid peroxidation and disease onset—mechanisms critically implicated in neurodegeneration. We also explore the potential interactions of lipofuscin with Aβ and their spatial location, and summarize evidence showing that lipofuscin may influence disease progression via feedback loops affecting cellular clearance and inflammation. Finally, we propose future research directions toward better understanding of the mechanisms of lipofuscin accumulation and improved lysosomal waste clearance in aging.

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The validity of Blue Zones demography: a response to critiques

Steven N Austad, PhD ✉, Giovanni M Pes, MD

Blue Zones are geographically and temporally defined areas with a history of disproportionately high concentrations of nonagenarians and centenarians. Nearly two decades ago, these zones gained international attention when the Blue Zone term was introduced in seminal articles published in *Experimental Gerontology* and *National Geographic*. Since then, numerous scientific papers have extracted valuable insights into human health from investigating the long-lived people who live there. However recently, validity of the ages of people living in the Blue Zones has been questioned. Here, we address these concerns by describing in detail the age validation process undertaken in Blue Zones and comparing it to the prevailing standards in gerontological demography. As discovered a century and a half ago, *most* self-reported claims of exceptional longevity are false. However, using methods developed by gerontological demographers over the past decades, the true age of people claiming exceptional longevity can be determined by cross-checking multiple independent documentary sources. This procedure minimizes, and usually eliminates, errors due to fraud, honest mistakes, poor memory, or identity switches, especially between homonymous siblings. All Blue Zones described herein have been extensively validated based on thoroughly cross-checked data from multiple independent sources plus state-of-the-art demographic methods. Consequently, age data from these Blue Zones are valid and reliable.

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COVID-19 mRNA Vaccination and 4-Year All-Cause Mortality Among Adults Aged 18 to 59 Years in France

Design, Setting, and Participants This cohort study used data from the French National Health Data System for all individuals in the French population aged 18 to 59 years who were alive on November 1, 2021. Data analysis was conducted from June 2024 to September 2025.

Exposure Exposure was defined as receiving a first mRNA dose between May 1 and October 31, 2021. Individuals who were unvaccinated by November 1, 2021, were assigned a random index date based on vaccinated individuals' vaccination dates.

Main Outcomes and Measures Cox models weighted for sociodemographic characteristics and 41 comorbidities were used to estimate 4-year all-cause mortality. Time to event was censored at all-cause death, COVID-19 vaccination for unexposed individuals, or study termination on March 31, 2025. Complementary analyses were performed, including a comparison of the main causes of death available up to December 31, 2023. Follow-up began 6 months after the index date in both groups to address immortal time bias. Short-term mortality within 6 months after vaccination was assessed in a separate, independent study using adapted self-controlled case series models.

Results A total of 22 767 546 vaccinated and 5 932 443 unvaccinated individuals were followed up for a median (IQR) of 45 (44-46) months. Vaccinated individuals were older than unvaccinated individuals (mean [SD] age, 38.0 [11.8] years vs 37.1 [11.4] years), more frequently women (11 688 603 [51.3%] vs 2 876 039 [48.5%]) and had more cardiometabolic comorbidities (2 126 250 [9.3%] vs 464 596 [7.8%]). During follow-up, 98 429 (0.4%) and 32 662 (0.6%) all-cause deaths occurred in the vaccinated and unvaccinated groups, respectively. Vaccinated individuals had a 74% lower risk of death from severe COVID-19 (weighted hazard ratio [wHR], 0.26 [95% CI, 0.22-0.30]) and a 25% lower risk of all-cause mortality (wHR, 0.75 [95% CI, 0.75-0.76]), with a similar association observed when excluding severe COVID-19 death. Sensitivity analysis revealed that vaccinated individuals consistently had a lower risk of death, regardless of the cause. Mortality was 29% lower within 6 months following COVID-19 vaccination (relative incidence, 0.71 [95% CI, 0.69-0.73]).

Conclusions and Relevance In this national cohort study of 28 million individuals, the results found no increased risk of 4-year all-cause mortality in individuals aged 18 to 59 years vaccinated against COVID-19, further supporting the safety of the mRNA vaccines that are widely used worldwide.

GLP- 1 Receptor Agonists in Patients with Cancer are Associated with Reduced All-Cause Mortality and Hospitalization

Background: GLP- 1 RA have been reported to decrease cancer incidence, but less is known about their potential in patients with active cancer. Preclinical studies have demonstrated that GLP-1 RA inhibit progression of solid tumor malignancies via downregulation of cellular proliferation pathways and improved glycemic control. Despite these promising findings, studies characterizing the effects of GLP-1 RA in patients with active cancer are limited.

Methods: Using TriNetX, a global database comprising over 120 million patients, we identified an overall cohort of 3747 patients with type 2 diabetes who received GLP-1 RA within 3 months of starting systemic therapy and identified 52,061 patients receiving metformin in the same timeframe as a control cohort. Additional sub-analyses stratified patients by hemoglobin A1c range, obesity, and by participants "newly started" on their first instance of GLP-1 RA within 3 months of starting cancer treatment.

Results: Patients receiving GLP-1 RA had significantly reduced mortality in both the overall monotherapy setting (HR: 0.875, 95% CI: (0.778-0.985), p=0.0268) and the new start setting (HR: 0.786 , 95% CI: (0.662-0.934), p= 0.0062) cohorts. Secondary analyses found lower rates of all-cause hospitalization, sepsis, major adverse cardiovascular events, pulmonary embolism, and pneumonia in patients on GLP-1 RA. Sub-analyses stratified by BMI and A1c did not meet statistical significance.

Conclusions: Patients with diabetes and cancer who received GLP-1 RA experienced superior survival outcomes and reduced rates of hospitalization compared to patients receiving metformin. Additionally, patients already on metformin and newly started on GLP-1 RA demonstrated superior survival outcomes compared to patients newly started on insulin. Further prospective, well-controlled studies are needed to evaluate the benefits of GLP-1 RA in patients with diabetes and cancer.

Somatic evolution following cancer treatment in normal tissue

The extent to which exogenous sources, including cancer treatment, contribute to somatic evolution in normal tissue remains unclear. Here we used high-depth duplex sequencing[1] (more than 30,000× coverage) to analyse 168 cancer-free samples representing 16 organs from 22 patients with metastatic cancer enroled in the PEACE research autopsy study. In every sample, we identified somatic mutations (range 305-2,854 mutations) at low variant allele frequencies (median 0.0000323). We extracted 16 distinct single-base substitution mutational signatures, reflecting processes that have moulded the genomes of normal cells. We identified alcohol-induced mutation acquisition in liver, smoking-induced mutagenesis in lung and cardiac tissue, and multiple treatment-induced processes, which correlated with therapy type and duration. Exogenous sources, including treatment, underpinned, on average, more than 40% of mutations in liver but less than 10% of mutations in brain samples. Finally, we observed tissue-specific selection, with positive selection in tissues such as lung (PTEN and PIK3CA), liver (NF2L2) and spleen (BRAF and NOTCH2), and limited selection in others, such as brain and cardiac tissue. More than 25% of driver mutations in normal tissue exposed to systemic anti-cancer therapy, including in TP53, could be attributed to treatment. Immunotherapy, although not associated with increased mutagenesis, was linked to driver mutations in PPM1D and TP53, illustrating how non-mutagenic treatment can sculpt somatic evolution. Our study reveals the rich tapestry of mutational processes and driver mutations in normal tissue, and the profound effect of lifetime exposures, including cancer treatment, on somatic evolution.

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Physical activity decreases cancer burden by alleviating immunosenescence-related inflammation and improving overall immunity

The associations between physical activity (PA) and the incidence and mortality of cancers and their underlying mechanisms remain largely unknown. Using mutually verifiable cohort studies with 443,768 adults in the United Kingdom and United States, we find that systemic inflammation, whose level increases with age, is dose-dependently associated with higher risks of eight inflammation-related cancers and all-cancer mortality. PA is dose-dependently associated with lower levels of systemic inflammation. Aerobic PA (117–500 min/week) is significantly associated with lower risks of inflammation-related cancers and all-cancer mortality. Single-cell sequencing, RNA sequencing, cytometry, and inflammation array show that aerobic exercise training downregulates immunosenescence-related gene expression, $Mki67^{+}$ immune cells, and pro-inflammatory molecules and upregulates anti-inflammatory factors, $Flt3^{+}$ immune cells, natural killers, and T lymphocytes in mice and hamsters, especially in older animals. These findings link exercise training to cancer risk reduction by alleviating inflammation, decreasing immunosenescence, and improving the reservoirs of overall immunity for cancer prevention.

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Aspirin prevents metastasis by limiting platelet TXA_2 suppression of T cell immunity

Metastasis is the spread of cancer cells from primary tumours to distant organs and is the cause of 90% of cancer deaths globally[1,2]. Metastasizing cancer cells are uniquely vulnerable to immune attack, as they are initially deprived of the immunosuppressive microenvironment found within established tumours[3]. There is interest in therapeutically exploiting this immune vulnerability to prevent recurrence in patients with early cancer at risk of metastasis. Here we show that inhibitors of cyclooxygenase 1 (COX-1), including aspirin, enhance immunity to cancer metastasis by releasing T cells from suppression by platelet-derived thromboxane A_2 (TXA_2). TXA_2 acts on T cells to trigger an immunosuppressive pathway that is dependent on the guanine exchange factor ARHGEF1, suppressing T cell receptor-driven kinase signalling, proliferation and effector functions. T cell-specific conditional deletion of *Arhgef1* in mice increases T cell activation at the metastatic site, provoking immune-mediated rejection of lung and liver metastases. Consequently, restricting the availability of TXA_2 using aspirin, selective COX-1 inhibitors or platelet-specific deletion of COX-1 reduces the rate of metastasis in a manner that is dependent on T cell-intrinsic expression of ARHGEF1 and signalling by TXA_2 in vivo. These findings reveal a novel immunosuppressive pathway that limits T cell immunity to cancer metastasis, providing mechanistic insights into the anti-metastatic activity of aspirin and paving the way for more effective anti-metastatic immunotherapies.

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Metabolic regulation of immunity in the tumor microenvironment

Metabolic-immune crosstalk in the tumor microenvironment (TME) is a critical driver of tumorigenesis, progression, and immune evasion. Tumor cells undergo profound metabolic reprogramming, causing nutrient competition, toxic metabolite accumulation, and the formation of cold niches that gradually exhaust effector immune cells. In contrast, immunosuppressive cells exhibit strong metabolic adaptability, reinforcing the suppressive milieu. Moreover, tertiary lymphoid structures provide nutrient- and oxygen-rich “moats” that sustain the functions of B and T cells. In addition, metabolic-immune interactions establish novel checkpoints through an “enzyme-metabolite-receptor” axis, which synergize with PD-1/CTLA-4 pathways to promote resistance to immune checkpoint inhibitors (ICIs). Although monotherapies with metabolic inhibitors have shown limited efficacy, their combination with ICIs is promising. Therefore, this review discusses the field from three perspectives: metabolic stress in the TME, immune cell adaptation, and targeting metabolic immune checkpoints in combination with immunotherapy.

Hepatic adaptation to chronic metabolic stress primes tumorigenesis

During chronic stress, cells must support both tissue function and their own survival. Hepatocytes perform metabolic, synthetic, and detoxification roles, but chronic nutrient imbalances can induce hepatocyte death and precipitate metabolic dysfunction-associated steatohepatitis (MASH, formerly NASH). Despite prior work identifying stress-induced drivers of hepatocyte death, chronic stress' functional impact on surviving cells remains unclear. Through cross-species longitudinal single-cell multi-omics, we show that ongoing stress drives prognostic developmental and cancer-associated programs in non-transformed hepatocytes while reducing their mature functional identity. Creating integrative computational methods, we identify and then experimentally validate master regulators perturbing hepatocyte functional balance, increasing proliferation under stress, and directly priming future tumorigenesis. Through geographic regression on human tissue microarray spatial transcriptomics, we uncover spatially structured multicellular communities and signaling interactions shaping stress responses. Our work reveals how cells' early solutions to chronic stress can prime future tumorigenesis and outcomes, unifying diverse modes of cellular dysfunction around core actionable mechanisms.

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Tattoo ink induces inflammation in the draining lymph node and alters the immune response to vaccination

Despite safety concerns regarding the toxicity of tattoo ink, no studies have reported the consequences of tattooing on the immune response. In this work, we have characterized the transport and accumulation of different tattoo inks in the lymphatic system using a murine model. Upon quick lymphatic drainage, we observed that macrophages mainly capture the ink in the lymph node (LN). An initial inflammatory reaction at local and systemic levels follows ink capture. Notably, the inflammatory process is maintained over time, as we observed clear signs of inflammation in the draining LN 2 mo following tattooing. In addition, the capture of ink by macrophages was associated with the induction of apoptosis in both human and murine models. Furthermore, the ink accumulated in the LN altered the immune response against two different types of vaccines. On the one hand, we observed a reduced antibody response following vaccination with an messenger ribonucleic acid (mRNA)-based severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine, which was associated with a decreased expression of the spike protein in macrophages in the draining LN. In contrast, we observed an enhanced response when vaccinated with influenza vaccine inactivated by ultraviolet (UV) radiation. Considering the unstoppable trend of tattooing in the population, our results are crucial in informing the toxicology programs, policymakers, and the general public regarding the potential risk of the tattooing practice associated with an altered immune response.

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What do you most hope we will achieve with mammalian synthetic biology within the next decade?

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