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Sven Bulterijs

Business/Conferences/ General news

Longevity Trends: March 2025

Sven Bulterijs

Introduction

This month, we take a deep dive into skin aging and explore ways to maintain a youthful appearance. When people think of skin aging, they often picture wrinkles, sagging, and pigmentation changes. While these are prominent features, aging skin undergoes many other transformations, including loss of lip fullness, the development of small dilated blood vessels (*spider veins*), and a reduction in fat tissue (Ng *et al.*, 2025).

Although this article focuses on the cosmetic aspects of skin aging, it is important to acknowledge its broader health implications. Aging skin is more susceptible to certain diseases, and many preventive measures that slow visible aging also reduce the risk of these conditions.

One well-documented risk factor is **UV exposure**, which significantly increases the likelihood of skin cancer. A single day in the sun can cause up to **100,000 UV-induced DNA damages per cell** (Hoeijmakers, 2009). Just **four tanning bed sessions per year** raise the risk of basal cell carcinoma by **15%** and squamous cell carcinoma by **11%** (Curti *et al.*, 2022). Additionally, experiencing **five or more sunburns doubles the risk of skin cancer** (D'Orazio *et al.*, 2013). UV radiation is estimated to be responsible for **65% of melanoma cases**—the deadliest form of skin cancer—and up to **90% of non-melanoma skin cancers** (D'Orazio *et al.*, 2013). Overall, skin cancer is among the most common cancers worldwide, with approximately **1.5 million new cases reported in 2022** (IARC, 2022).

Beyond skin cancer, aging also **impairs wound healing**, a problem further exacerbated by smoking. Cigarette smoking accelerates visible skin aging while simultaneously reducing the skin's ability to repair itself.

By understanding the mechanisms of skin aging and adopting protective habits, one can not only maintain a youthful appearance but also promote overall skin health and longevity.

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Insilico Medicine raises $110M for new trials and robotic helping hands

By **Conor Hale** · Mar 12, 2025 11:00am

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Eli Lilly's Alzheimer's contender Kisunla gets thumbs down from EU regulators over safety concerns

By **Zoey Becker** · Mar 28, 2025 11:36am

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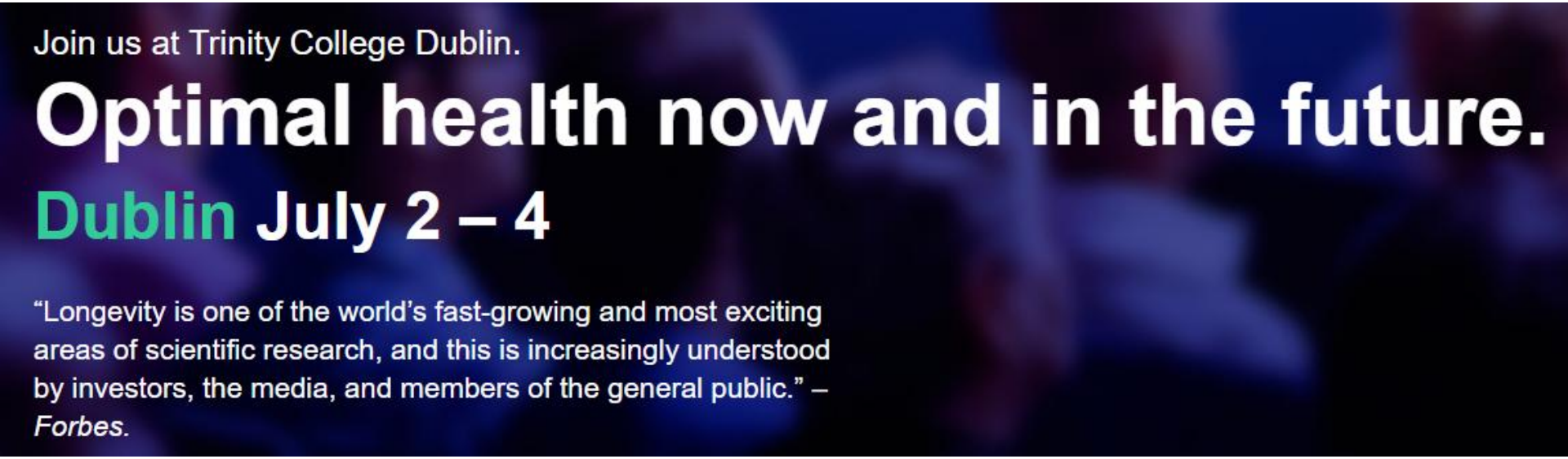
Paralysed man stands again after receiving 'reprogrammed' stem cells

Another man also regained some movement, but two others experienced minimal improvement.

Upcoming conferences

I'll be there!



Aging research articles

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5-HT_{2C} agonism as a neurotherapeutic for sarcopenia: preclinical proof of concept

Sarcopenia, the pathological age-related loss of muscle mass and strength, contributes to physical decline, frailty, and diminished healthspan. The impact of sarcopenia is expected to rise as the aging population grows, and treatments remain limited. Therefore, novel approaches for enhancing physical function and strength in older adults are desperately needed. Recent evidence suggests that deficits in motor neuron excitability contribute significantly to age-related weakness. Accordingly, we hypothesized that enhancing motor neuron excitability could be a novel strategy for mitigating age-related declines in physical function and strength. To test this hypothesis, we targeted the 5-HT_{2C} receptor with an agonist, as this receptor is known to enhance intrinsic excitability and amplify persistent inward currents of motor neurons. We found that a single oral gavage dose of 1.5, 3, and 6 mg/kg lorcaserin, a selective 5-HT_{2C} agonist, significantly increased indices of motor neuron excitability (e.g., cervical motor evoked potential (cMEP) amplitude by 53–64% and reduced attenuation in cMEP amplitude during repetitive stimulation), along with improvements in motor coordination (22–24% enhancement in rotarod performance) and functional strength (~17% increase in max weighted cart pull and 12% increase in grip strength) in aged mice. In contrast, antagonism of 5-HT_2 receptors resulted in the opposite effect, reducing cMEP amplitude by ~26%, increasing attenuation of cMEP amplitude during repetitive stimulation, and decreasing grip strength by ~10% in aged mice. Overall, our findings indicate that enhancing motor neuron excitability via 5-HT_{2C} agonism holds promise as a neurotherapeutic approach to treat age-related motor decline and sarcopenia.

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Multi-omic profiling of sarcopenia identifies disrupted branched-chain amino acid catabolism as a causal mechanism and therapeutic target

Sarcopenia is a geriatric disorder characterized by a gradual loss of muscle mass and function. Despite its prevalence, the underlying mechanisms remain unclear, and there are currently no approved treatments. In this study, we conducted a comprehensive analysis of the molecular and metabolic signatures of skeletal muscle in patients with impaired muscle strength and sarcopenia using multi-omics approaches. Across discovery and replication cohorts, we found that disrupted branched-chain amino acid (BCAA) catabolism is a prominent pathway in sarcopenia, which leads to BCAA accumulation and decreased muscle health. Machine learning analysis further supported the causal role of BCAA catabolic dysfunction in sarcopenia. Using mouse models, we validated that defective BCAA catabolism impairs muscle mass and strength through dysregulated mTOR signaling, and enhancing BCAA catabolism by BT2 protects against sarcopenia in aged mice and in mice lacking *Ppm1k*, a positive regulator of BCAA catabolism in skeletal muscle. This study highlights improving BCAA catabolism as a potential treatment of sarcopenia.

Bcl−xL overexpression in T cells preserves muscle mitochondrial structure and function and prevents frailty in old mice

Our previous transcriptomic analysis revealed an up-regulation of the antiapoptotic protein B cell lymphoma-extra large (Bcl-xL) in centenarians relative to octogenarians or younger cohorts. In this study, we used Bcl-xL-overexpressing mice to assess its impact on successful aging. Our findings indicate that Bcl-xL overexpression modifies T cell subsets and improves their metabolism, apoptosis resistance, macroautophagy, and cytokine production during aging. This more resilient immune system reduces inflammation and preserves mitochondrial integrity and function in muscle tissue, thereby retarding the onset of frailty. These results underscore the important contribution of Bcl-xL to healthy aging, a phenomenon that is conserved across mammalian species.

SIRT5 safeguards against primate skeletal muscle ageing via desuccinylation of TBK1

Ageing-induced skeletal muscle deterioration contributes to sarcopenia and frailty, adversely impacting the quality of life in the elderly. However, the molecular mechanisms behind primate skeletal muscle ageing remain largely unexplored. Here, we show that SIRT5 expression is reduced in aged primate skeletal muscles from both genders. SIRT5 deficiency in human myotubes hastens cellular senescence and intensifies inflammation. Mechanistically, we demonstrate that TBK1 is a natural substrate for SIRT5. SIRT5 desuccinylates TBK1 at lysine 137, which leads to TBK1 dephosphorylation and the suppression of the downstream inflammatory pathway. Using SIRT5 lentiviral vectors for skeletal muscle gene therapy in male mice enhances physical performance and alleviates age-related muscle dysfunction. This study sheds light on the molecular underpinnings of skeletal muscle ageing and presents the SIRT5-TBK1 pathway as a promising target for combating age-related skeletal muscle degeneration.

Mito-Modulatory Medication Use and Skeletal Muscle Bioenergetics Among Older Men and Women: the Study of Muscle, Mobility and Aging

Background

The potential impacts of drug-induced modulation of mitochondrial function in humans remain unclear despite the high prevalence of "mito-modulatory" medication use among older adults. While these medications, such as statins and metformin, have undergone extensive characterization of their effects on mitochondrial function in vitro, the effects in humans are far more complex and poorly understood.

Methods

This study uses data from the Study of Muscle, Mobility and Aging (SOMMA) to evaluate how mito-modulatory medication use is related to skeletal muscle bioenergetic capacity, measured by ex vivo high-resolution respirometry and in vivo phosphorus magnetic resonance spectroscopy in healthy older adults.

Results

We found that mito-modulatory medication use was related to lower maximal complex I&II supported oxidative phosphorylation (Max OXPHOS), maximal electron transfer system capacity (Max ETS), and maximal ATP production capacity (ATP Max) in men, but not in women. We also found this to be dependent on the number of medications used, in which higher mito-modulatory medication load was associated with lower Max OXPHOS, Max ETS, and ATP Max.

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Metformin and physical performance in older people with probable sarcopenia and physical prefrailty or frailty in England (MET-PREVENT): a double-blind, randomised, placebo-controlled trial

Methods

In this double-blind, randomised, parallel-group, placebo-controlled trial (MET-PREVENT), participants aged 65 years and older with a 4-m walk speed of less than 0·8 m/s and probable sarcopenia, characterised by low handgrip strength (<16 kg for women and <27 kg for men) or five times sit-to-stand time of longer than 15 s (or inability to complete five sit-to-stands) were recruited from primary care and hospital clinics in Gateshead and Newcastle, UK. Participants were randomly assigned (1:1), via a web-based system with minimisation to ensure balance by sex and baseline 4-m walk speed, to receive either 500 mg oral metformin or matching placebo three times a day for 4 months. The primary outcome was the adjusted between-group difference in 4-m walk speed at 4 months. The primary outcome was analysed in the intention-to-treat population (ie, all participants randomly assigned to treatment) who had complete data, and safety was assessed in all participants who received at least one dose of study treatment. This study is registered with the ISRCTN registry, ISRCTN29932357, and is now complete.

Findings

Between Aug 1, 2021, and Sept 30, 2022, 268 individuals were screened for inclusion in the trial, and 72 participants were randomly assigned to either metformin (n=36) or placebo (n=36; intention-to-treat population). Mean age was 80·4 years (SD 5·7), 42 (58%) of 72 participants were female, 30 (42%) were male, and 70 (97%) were White British. 70 (97%) of 72 participants had complete follow-up data (n=34 in the metformin group and n=36 in the placebo group). Mean 4-m walk speed at 4 months was 0·57 m/s (SD 0·19) in the metformin group and 0·58 m/s (0·24) in the placebo group (adjusted treatment effect 0·001 m/s [95% CI −0·06 to 0·06]; p=0·96). 108 adverse events occurred in 35 (100%) of 35 participants who received metformin and 77 adverse events occurred in 33 (92%) of 36 participants who received placebo, and 12 (34%) of 35 participants had hospital admissions in the metformin group versus three (8%) of 36 participants in the placebo group. One death occurred, in the metformin group (one [3%] of 35), and was judged to be unrelated to study treatment.

A pilot study of senolytics to improve cognition and mobility in older adults at risk for Alzheimer's disease

Background

This single-arm study evaluates the feasibility, safety, and preliminary effects of two senolytic agents, Dasatinib and Quercetin (DQ), in older adults at risk of Alzheimer's disease.

Methods

Participants took 100 mg of Dasatinib and 1250 mg of Quercetin for two days every two weeks over 12 weeks. Recruitment rate, adverse events, absolute changes in functional outcomes, and percent changes in biomarkers were calculated. Spearman correlations between functional and biomarker outcomes were performed.

Findings

Approximately 10% of telephone-screened individuals completed the intervention (n = 12). There were no serious adverse events related to the intervention. Mean Montreal Cognitive Assessment (MoCA) scores non-significantly increased following DQ by 1.0 point (95% CI: −0.7, 2.7), but increased significantly by 2.0 points (95% CI: 0.1, 4.0) in those with lowest baseline MoCA scores. Mean percent change in tumour necrosis factor-alpha (TNF-α), a key product of the senescence-associated secretory phenotype (SASP), non-significantly decreased following DQ by −3.0% (95% CI: −13.0, 7.1). Changes in TNF-α were significantly and inversely correlated with changes in MoCA scores ($r = -0.65$, $p = 0.02$), such that reductions in TNF- α were correlated with increases in MoCA scores.

Interpretation

This study suggests that intermittent DQ treatment is feasible and safe; data hint at potential functional benefits in older adults at risk of Alzheimer's disease. The observed reduction in TNF-α and its correlation with increases in MoCA scores suggests that DQ may improve cognition by modulating the SASP. However, there was not an appropriate control group. Data are preliminary and must be interpreted cautiously.

A Phase IIa clinical trial to evaluate the effects of anti-retroviral therapy in Alzheimer's disease (ART-AD)

Retrotransposons constitute over 40% of the human genome. Studies in *Drosophila*, mice, cultured cells, and human brain show that retrotransposons are activated in tauopathies, including Alzheimer's disease, and causally drive neurodegeneration. The reverse transcriptase inhibitor 3TC (lamivudine) reduces retrotransposon activation and suppresses tau neurotoxicity among model systems. This phase 2a open-label trial (Pilot Study to Investigate the Safety and Feasibility of Anti-Retroviral Therapy for Alzheimer's Disease, NCT04552795, registered 09/10/2020) followed 12 participants with early Alzheimer's disease (MMSE > 24, CDR = 0.5) over 24 weeks to assess safety, tolerability, and feasibility of daily 300 mg 3TC treatment. The sample was well-educated (12-20 years) and culturally diverse (25% from underrepresented groups). In addition to a favorable safety profile and stable cognitive measures, notable significant changes in fluid-based biomarkers include reduction of glial fibrillary acidic protein (GFAP) ($P = 0.03$) in CSF, suggestive of reduced neuroinflammation, and elevation of Aβ42/40 ($P = 0.009$) in plasma, suggestive of reduced plaque load in the brain. These results warrant further exploration in a larger, placebo-controlled trial.

A Brain-Penetrating Foldamer Rescues Aβ Aggregation-Associated Alzheimer's Disease Phenotypes in *In Vivo* Models

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that is the leading cause of dementia, affecting nearly 55 million people across the world. One of the central pathological factors associated with AD is the aggregation of $A\beta_{42}$, a peptide product cleaved through pathological processes in AD. Under pathological conditions, $A\beta_{42}$ aggregates into insoluble plaques in the brain and impairs the function of neurons, which contributes to the cognitive decline associated with AD. Therefore, the modulation of $A\beta_{42}$ aggregation is considered a potential therapeutic intervention for AD. Using an Oligoquinoline-based foldamer library, we have identified a potent foldamer antagonist (SK-131) of $A\beta_{42}$ aggregation. SK-131 inhibits the aggregation by inducing a α-helical structure in monomeric $A\beta_{42}$. Here, we demonstrated that SK-131 rescues $A\beta_{42}$ aggregation-associated phenotypes in AD cellular and multiple *Caenorhabditis elegans* AD models, including intracellular inhibition of $A\beta_{42}$ aggregation, rescue of behavioral deficits, and attenuation of reactive oxygen species. It efficiently crosses the blood-brain barrier and demonstrates favorable pharmaceutical properties. It also potently inhibits Zn^{2+}-mediated $A\beta_{42}$ aggregation by potentially displacing Zn^{2+} from $A\beta_{42}$. In summary, we have identified a potent brain-penetrating foldamer that efficiently rescues AD phenotypes in *in vivo* models. Unlike most of the therapeutic approaches that target Aβ aggregates, we have identified and validated a novel therapeutic pathway by inducing structural change in Aβ and rescuing AD phenotypes in *in vivo* models. This study will further aid in the quest to identify lead therapeutics to slow or stop the progression of AD.

Aβ–driven nuclear pore complex dysfunction alters activation of necroptosis proteins in a mouse model of Alzheimer's disease

The emergence of Aβ pathology is one of the hallmarks of Alzheimer's disease (AD), but the mechanisms and impact of Aβ in progression of the disease is unclear. The nuclear pore complex (NPC) is a multi-protein assembly in mammalian cells that regulates movement of macromolecules across the nuclear envelope; its function is shown to undergo age-dependent decline during normal aging and is also impaired in multiple neurodegenerative disorders. Yet not much is known about the impact of Aβ on NPC function in neurons. Here, we examined NPC and nucleoporin (NUP) distribution and nucleocytoplasmic transport using a mouse model of AD ($App^{NL\text{-}G\text{-}F/NL\text{-}G\text{-}F}$) that expresses Aβ in young animals. Our studies revealed that a time-dependent accumulation of intracellular Aβ corresponded with a reduction of NPCs and NUPs in the nuclear envelope which resulted in the degradation of the permeability barrier and inefficient segregation of nucleocytoplasmic proteins, and active transport. As a result of the NPC dysfunction *App* KI neurons become more vulnerable to inflammation-induced necroptosis - a programmed cell death pathway where the core components are activated via phosphorylation through nucleocytoplasmic shutting. Collectively, our data implicates Aβ in progressive impairment of nuclear pore function and further confirms that the protein complex is vulnerable to disruption in various neurodegenerative diseases and is a potential therapeutic target.

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Modulating mTOR-dependent astrocyte substate transitions to alleviate neurodegeneration

Traditional approaches to studying astrocyte heterogeneity have mostly focused on analyzing static properties, failing to identify whether subtypes represent intermediate or final states of reactive astrocytes. Here we show that previously proposed neuroprotective and neurotoxic astrocytes are transitional states rather than distinct subtypes, as revealed through time-series multiomic sequencing. Neuroprotective astrocytes are an intermediate state of the transition from a nonreactive to a neurotoxic state in response to neuroinflammation, a process regulated by the mTOR signaling pathway. In Alzheimer's disease (AD) and aging, we observed an imbalance in neurotoxic and neuroprotective astrocytes in animal models and human patients. Moreover, targeting mTOR in astrocytes with rapamycin or shRNA mitigated astrocyte neurotoxic effects in neurodegenerative mouse models. Overall, our study uncovers a mechanism through which astrocytes exhibit neuroprotective functions before becoming neurotoxic under neuroinflammatory conditions and highlights mTOR modulation specifically in astrocytes as a potential therapeutic strategy for neurodegenerative diseases.

Blood N-glycomics reveals individuals at risk for cognitive decline and Alzheimer's disease

Background

Blood biomarkers with prognostic accuracy for Alzheimer's disease (AD) are crucial for selecting at-risk individuals for interventions. Altered protein N-glycosylation has been implicated in several pathogenic pathways in AD and could be an early AD biomarker.

Methods

We developed a mass spectrometry-based method to simultaneously quantify 62 blood N-glycan structures in individuals with biological or clinical AD and matched controls. We analysed N-glycan levels in a Swedish discovery cohort (n = 40) and validated our results in a Norwegian cohort (n = 60). Individuals were grouped according to N-glycan levels using unsupervised hierarchical clustering. Difference in disease progression between groups were modelled using linear mixed-effects models.

Findings

A subgroup of individuals exhibited low blood N-glycosylation (32.4% of Swedish cohort, 37.9% of Norwegian cohort). In the Swedish cohort, low N-glycosylation was associated with AD and cognitive decline. In the Norwegian cohort, low blood N-glycosylation showed no correlation with amyloid/tau, but importantly, strongly predicted future cognitive decline. In total, fourteen N-glycan structures were significantly less abundant in the low N-glycosylation group compared to the rest of the individuals in both cohorts.

Interpretation

Reduced blood N-glycan levels predict cognitive decline independent of amyloid or tau status. Blood N-glycome profiling could be used to identify individuals at risk for AD dementia.

Deep learning to quantify the pace of brain aging in relation to neurocognitive changes

Chenzhong Yin, Phoebe Imms, Nahian F. Chowdhury, +5, and the Alzheimer's Disease Neuroimaging Initiative Authors Info & Affiliations

Brain age (BA), distinct from chronological age (CA), can be estimated from MRIs to evaluate neuroanatomic aging in cognitively normal (CN) individuals. BA, however, is a cross-sectional measure that summarizes cumulative neuroanatomic aging since birth. Thus, it conveys poorly recent or contemporaneous aging trends, which can be better quantified by the (temporal) pace *P* of brain aging. Many approaches to map *P*, however, rely on quantifying DNA methylation in whole-blood cells, which the blood–brain barrier separates from neural brain cells. We introduce a three-dimensional convolutional neural network (3D-CNN) to estimate *P* noninvasively from longitudinal MRI. Our longitudinal model (LM) is trained on MRIs from 2,055 CN adults, validated in 1,304 CN adults, and further applied to an independent cohort of 104 CN adults and 140 patients with Alzheimer's disease (AD). In its test set, the LM computes *P* with a mean absolute error (MAE) of 0.16 y (7% mean error). This significantly outperforms the most accurate cross-sectional model, whose MAE of 1.85 y has 83% error. By synergizing the LM with an interpretable CNN saliency approach, we map anatomic variations in regional brain aging rates that differ according to sex, decade of life, and neurocognitive status. LM estimates of *P* are significantly associated with changes in cognitive functioning across domains. This underscores the LM's ability to estimate *P* in a way that captures the relationship between neuroanatomic and neurocognitive aging. This research complements existing strategies for AD risk assessment that estimate individuals' rates of adverse cognitive change with age.

Blocking the Dkk1-LRP6 interaction prevents acute amyloid-β-driven cognitive impairment

Synapse loss driven by amyloid-β (Aβ) is an early event in Alzheimer's disease (AD). Although the mechanism by which Aβ drives synapse loss remain poorly understood data indicate that a disruption of Wnt signalling plays an important part. We have shown that Aβ exerts its effects on synapses through Dickkopf-1 (Dkk1), a secreted protein that acts upon Wnt signalling *via* a direct interaction with the canonical Wnt pathway co-receptor proteins, LRP5 and LRP6, preventing their interaction with the receptor Frizzled. This antagonises canonical, Wnt/β-catenin, signalling and allows concomitant activation of non-canonical signalling pathways. We contend that it is the switch from canonical to non-canonical Wnt signalling activity that drives synapse loss and subsequent cognitive impairment in AD, driven by Aβ and mediated by Dkk1. Preventing the Dkk1-LRP5/6 interaction could protect synapses and cognition against Aβ by maintaining canonical Wnt signalling. To test this, we mapped the Dkk1-LRP6 interaction by peptide array and identified a small peptide able to disrupt the Dkk1-LRP6 interaction. This Dkk1-LRP6 'disruptor' peptide dose dependently restores canonical Wnt signalling in the presence of Dkk1; blocks Dkk1-driven dendritic spine loss in primary rat cortical cultures and the accompanying increase in endogenous Aβ production; and when administered intracerebroventricularly to a rat acute Aβ model, blocks Aβ-driven cognitive impairment. These data support our contention that the ability of Aβ to induce Dkk1 and the effects of Dkk1 on LRP6 are an important element in AD aetiopathology and establish Dkk1 as a therapeutic target for protecting synapse and cognition in AD.

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Parallel patterns of age-related working memory impairment in marmosets and macaques

As humans age, some experience cognitive impairment while others do not. When impairment does occur, it is not expressed uniformly across cognitive domains and varies in severity across individuals. Translationally relevant model systems are critical for understanding the neurobiological drivers of this variability, which is essential to uncovering the mechanisms underlying the brain's susceptibility to the effects of aging. As such, non-human primates (NHPs) are particularly important due to shared behavioral, neuroanatomical, and age-related neuropathological features with humans. For many decades, macaque monkeys have served as the primary NHP model for studying the neurobiology of cognitive aging. More recently, the common marmoset has emerged as an advantageous model for this work due to its short lifespan that facilitates longitudinal studies. Despite their growing popularity as a model, whether marmosets exhibit patterns of age-related cognitive impairment comparable to those observed in macaques and humans remains unexplored. To address this major limitation for the development and evaluation of the marmoset as a model of cognitive aging, we directly compared working memory ability as a function of age in macaques and marmosets on the identical task. We also implemented varying delays to further tax working memory capacity. Our findings demonstrate that marmosets and macaques exhibit remarkably similar age-related working memory deficits, with macaques performing better than marmosets on longer delays. These results highlight the similarities and differences between the two most commonly used NHP models and support the value of the marmoset as a model for cognitive aging research within the neuroscience community.

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Widespread Multimorbidity in a Cohort of Aging, Radiation-exposed Rhesus Macaques

Delayed effects of acute radiation exposure (DEARE) and radiation late effects are a suite of conditions that become apparent months to years after initial exposure to radiation in both humans and non-human primates. Many of these disorders, including cardiac complications, insulin resistance, bone loss, hypertension, and others, are also more common among aging cohorts independent of radiation exposure. This study characterized disease incidence, age of onset, and multimorbidity for 20 common, chronic diseases in 226 irradiated and 51 control rhesus macaques (Macaca mulatta) from the Wake Forest Non-Human Primate Radiation Late Effects Cohort (RLEC) to identify the excess risk of chronic disease caused by radiation-induced tissue damage. Irradiated animals were exposed to 4.0-8.5 Gy of ionizing radiation (mean 6.17 ± 1.29 Gy) one year on average prior to joining the cohort. In addition to the acute impact of early-life irradiation, these animals have been aging postirradiation for up to 15 years (mean 5.2 ± 3.0 years). Lifespan is an average of 5.1 years shorter in irradiated animals and radiation is associated with significantly increased rates of periodontitis, cataracts, testicular atrophy, tumors, diabetes, and brain lesions. While most of these chronic diseases occur in non-irradiated macaques, irradiated animals have significantly earlier age of onset for periodontitis, cataracts, bone loss, being overweight, and arthritis. This accelerated onset leads to 2.9 ± 1.9 comorbid conditions among irradiated animals compared to 1.9 ± 1.2 diagnoses among controls by young adulthood (age 8) and 5.2 ± 2.4 compared to 3.4 ± 1.8 conditions by middle age (15 years). Subsets of these comorbid conditions cluster among animals with fibrosis-related disorders (diabetes, lung injury, liver disease, kidney disease, heart disease, and tumors) commonly diagnosed together independent of prevalence. A second cluster of comorbidities centers around bone loss and is associated with being underweight and female reproductive problems. While there are significant differences in disease burden between irradiated and control animals, there was no dose effect of radiation on lifespan, age to first diagnosis, or comorbidities and substantial heterogeneity across each of these measures. This underlying heterogeneity in response to radiation suggests the existence of a yet unidentified determinant of resilience.

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PREPRINT

Canonical Wnt/β-catenin signalling regulates inducible aging and regeneration loss in hydra

Freshwater cnidarians from the genus Hydra have exceptional regeneration capacities and show negligible aging. However, one species, Hydra oligactis, experiences accelerated senescence following sexual reproduction, characterized by regeneration loss, stem cell depletion, reduced body size, motility and food capture rates. This phenomenon, termed inducible aging, is triggered by temperature-induced sexual reproduction. The physiological regulation of the switch from high regenerative capacity and low senescence to regeneration loss and accelerated aging remain largely unexplored. By comparing gene expression patterns of asexual and sexual polyps following amputation we identified several canonical Wnt/β-catenin signalling pathway transcripts that showed differential expression in the regeneration-deficient sexual individuals, suggesting the involvement of this pathway in the inducible aging phenotype. Pharmacological activation of canonical Wnt/β-catenin signalling with alsterpaullone (ALP) restored head regeneration and improved survival of animals. To find out more about the role of this pathway in sexual development and post-reproductive senescence, we treated animals in various stages of egg maturation with ALP. We found that ALP delayed egg maturation when applied in early stages, but had smaller effects when applied in later stages of gametogenesis, without having a stark effect on overall fecundity. ALP treatment increased survival following sexual reproduction. These results show that the canonical Wnt/β-catenin signalling pathway regulates reproduction, regeneration and post-reproductive senescence in H. oligactis.

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Age-dependent cytokine surge in blood precedes cancer diagnosis

Guangbo Chen, Azam Mohsin, Hong Zheng, +10, and Mark M. Davis Authors Info & Affiliations

Aging is associated with increased variability and dysregulation of the immune system. We performed a system-level analysis of serum cytokines in a longitudinal cohort of 133 healthy individuals over 9 y. We found that cancer incidence is a major contributor to increased cytokine abundance variability. Circulating cytokines increase up to 4 y before a cancer diagnosis in subjects with age over 80 y. We also analyzed cytokine expression in 10 types of early-stage cancers from The Cancer Genome Atlas. We found that a similar set of cytokines is upregulated in tumor tissues, specifically after the age of 80 y. Similarly, cellular senescence activity and CDKN1A/p21 expression increase with age in cancer tissues. Finally, we demonstrated that the cytokine levels in serum can be used to predict cancers among subjects age at 80+ y. Our results suggest that latent senescent cancers contribute to age-related chronic inflammation.

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The Rich Evolutionary History of the Reactive Oxygen Species Metabolic Arsenal Shapes Its Mechanistic Plasticity at the Onset of Metazoan Regeneration

Regeneration, the ability to restore body parts after injury, is widespread in metazoans; however, the underlying molecular and cellular mechanisms involved in this process remain largely unknown, and its evolutionary history is consequently unresolved. Recently, reactive oxygen species (ROS) have been shown in several metazoan models to be triggers of apoptosis and cell proliferation that drive regenerative success. However, it is not known whether the contribution of ROS to regeneration relies on conserved mechanisms. Here we performed a comparative genomic analysis of ROS metabolism actors across metazoans, and carried out a comparative study of the deployment and roles of ROS during regeneration in two different metazoan models: the annelid *Platynereis dumerilii* and the cnidarian *Nematostella vectensis*. We established that the vast majority of metazoans encode a core redox kit allowing for the production and detoxification of ROS, and overall regulation of ROS levels. However, the precise composition of the redox arsenal can vary significantly from species to species, suggesting that evolutionary constraints apply to ROS metabolism functions rather than precise actors. We found that while ROS are necessary for regeneration in both *Platynereis* and *Nematostella*, the two species deploy different enzymatic activities controlling ROS dynamics, and display distinct effects of ROS signaling on injury-induced apoptosis and cell proliferation. We conclude that, while ROS are a common feature of metazoan regeneration, their production and contribution to this phenomenon may depend on different molecular mechanisms highlighting the overall plasticity of the machinery.

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Proteome Size Is Positively Correlated with Lifespan in Mammals but Negatively Correlated with Lifespan in Birds

Juliano Morimoto ✉, Zuzanna Pietras

The central dogma describes the unidirectional flow of genetic information from DNA to proteins, leading to an underappreciation of the potential for the information contained in proteomes (the full set of proteins in an organism) to reflect broader biological processes such as lifespan. Here, this is addressed by examining how the size and composition of 276 proteomes from four vertebrate classes are related to lifespan. After accounting for the relationship between body weight and lifespan, lifespan is negatively correlated with proteome size in birds and, to a weaker extent, in fish, and positively correlated with lifespan in mammals. Proteome composition varies amongst the four vertebrate classes, but there is no evidence that any specific amino acid correlated with lifespan. The findings in relation to the role of dietary amino acid restriction are discussed on lifespan extension and raise questions about evolutionary and structural forces shaping proteome composition across species.

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Clonal dynamics and somatic evolution of haematopoiesis in mouse

Haematopoietic stem cells maintain blood production throughout life[1]. Although extensively characterized using the laboratory mouse, little is known about clonal selection and population dynamics of the haematopoietic stem cell pool during murine ageing. We isolated stem cells and progenitors from young and old mice, identifying 221,890 somatic mutations genome-wide in 1,845 single-cell-derived colonies. Mouse stem cells and progenitors accrue approximately 45 somatic mutations per year, a rate only approximately threefold greater than human progenitors despite the vastly different organismal sizes and lifespans. Phylogenetic patterns show that stem and multipotent progenitor cell pools are established during embryogenesis, after which they independently self-renew in parallel over life, evenly contributing to differentiated progenitors and peripheral blood. The stem cell pool grows steadily over the mouse lifespan to about 70,000 cells, self-renewing about every 6 weeks. Aged mice did not display the profound loss of clonal diversity characteristic of human haematopoietic ageing. However, targeted sequencing showed small, expanded clones in the context of murine ageing, which were larger and more numerous following haematological perturbations, exhibiting a selection landscape similar to humans. Our data illustrate both conserved features of population dynamics of blood and distinct patterns of age-associated somatic evolution in the short-lived mouse.

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Tracking clusterin expression in hematopoietic stem cells reveals their heterogeneous composition across the lifespan

Hematopoietic stem cells (HSCs) exhibit significant age-related phenotypic and functional alterations. Although single-cell technologies have elucidated age-related compositional changes, prospective identification of aging-associated HSC subsets has remained challenging. In this study, utilizing Clusterin (Clu)-GFP reporter mice, we demonstrated that Clu expression faithfully marks age-associated myeloid/platelet-biased HSCs throughout life. Clu-GFP expression clearly segregates a novel age-associated HSC subset that overlaps with but is distinct from those previously identified using antibodies against aging maker proteins or reporter systems of aged HSC signature genes. Clu-positive (Clu+) HSCs emerge as a minor population in the fetus and progressively expand with age. Clu+ HSCs display not only an increased propensity for myeloid/platelet-biased differentiation but also a unique behaviour in the BM, favouring self-renewal over differentiation into downstream progenitors. In contrast, Clu-negative (Clu-) HSCs exhibit lineage-balanced differentiation, which predominates in the HSC pool during development but becomes underrepresented as aging progresses. Both subsets maintain long-term self-renewal capabilities even in aged mice but contribute differently to hematopoiesis. The predominant expansion of Clu+ HSCs largely drives the age-related changes observed in the HSC pool. Conversely, Clu- HSCs preserve youthful functionality and molecular characteristics into old age. Consequently, progressive changes in the balance between Clu+ and Clu- HSC subsets account for HSC aging. Our findings establish Clu as a novel marker for identifying aging-associated changes in HSCs and provide a new approach that enables lifelong tracking of the HSC aging process.

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Life-long microbiome rejuvenation improves intestinal barrier function and inflammaging in mice

Background: Alterations in the composition and function of the intestinal microbiota have been observed in organismal aging across a broad spectrum of animal phyla. Recent findings, which have been derived mostly in simple animal models, have even established a causal relationship between age-related microbial shifts and lifespan, suggesting microbiota-directed interventions as a potential tool to decelerate aging processes. To test whether a life-long microbiome rejuvenation strategy could delay or even prevent aging in non-ruminant mammals, we performed recurrent fecal microbial transfer (FMT) in mice throughout life. Transfer material was either derived from 8-week-old mice (young microbiome, yMB) or from animals of the same age as the recipients (isochronic microbiome, iMB) as control. Motor coordination and strength were analyzed by rotarod and grip strength tests, intestinal barrier function by serum LAL assay, transcriptional responses by single-cell RNA sequencing, and fecal microbial community properties by 16S rRNA gene profiling and metagenomics.

Results: Colonization with yMB improved coordination and intestinal permeability compared to iMB. yMB encoded fewer pro-inflammatory factors and altered metabolic pathways favoring oxidative phosphorylation. Ecological interactions among bacteria in yMB were more antagonistic than in iMB implying more stable microbiome communities. Single-cell RNA sequencing analysis of intestinal mucosa revealed a salient shift of cellular phenotypes in the yMB group with markedly increased ATP synthesis and mitochondrial pathways as well as a decrease of age-dependent mesenchymal hallmark transcripts in enterocytes and TA cells, but reduced inflammatory signaling in macrophages.

Conclusions: Taken together, we demonstrate that life-long and repeated transfer of microbiota material from young mice improved age-related processes including coordinative ability (rotarod), intestinal permeability, and both metabolic and inflammatory profiles mainly of macrophages but also of other immune cells. Video Abstract.

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Rejuvenation of Senescent Cells, In Vitro and In Vivo, by Low-Frequency Ultrasound

The presence of senescent cells causes age-related pathologies since their removal by genetic or pharmacological means, as well as possibly by exercise, improves outcomes in animal models. An alternative to depleting such cells would be to rejuvenate them to promote their return to a replicative state. Here we report that treatment of non-growing senescent cells with low-frequency ultrasound (LFU) rejuvenates the cells for growth. Notably, there are 15 characteristics of senescent cells that are reversed by LFU, including senescence-associated secretory phenotype (SASP) plus decreased cell and organelle motility. There is also inhibition of β-galactosidase, p21, and p16 expression, telomere length is increased, while nuclear 5mC, H3K9me3, γH2AX, nuclear p53, ROS, and mitoSox levels are all restored to normal levels. Mechanistically, LFU causes Ca^{2+} entry and increased actin dynamics that precede dramatic increases in autophagy and an inhibition of mTORC1 signaling plus movement of Sirtuin1 from the nucleus to the cytoplasm. Repeated LFU treatments enable the expansion of primary cells and stem cells beyond normal replicative limits without altering phenotype. The rejuvenation process is enhanced by co-treatment with cytochalasin D, rapamycin, or Rho kinase inhibition but is inhibited by blocking Sirtuin1 or Piezo1 activity. Optimized LFU treatment parameters increased mouse lifespan and healthspan. These results indicate that mechanically induced pressure waves alone can reverse senescence and aging effects at the cellular and organismal level, providing a non-pharmacological way to treat the effects of aging.

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Reprogramming to restore youthful epigenetics of senescent nucleus pulposus cells for mitigating intervertebral disc degeneration and alleviating low back pain

Aging is a pivotal risk factor for intervertebral disc degeneration (IVDD) and chronic low back pain (LBP). The restoration of aging nucleus pulposus cells (NPCs) to a youthful epigenetic state is crucial for IVDD treatment, but remains a formidable challenge. Here, we proposed a strategy to partially reprogram and reinstate youthful epigenetics of senescent NPCs by delivering a plasmid carrier that expressed pluripotency-associated genes (*Oct4*, *Klf4* and *Sox2*) in Cavin2-modified exosomes (OKS@M-Exo) for treatment of IVDD and alleviating LBP. The functional OKS@M-Exo efficaciously alleviated senescence markers ($p16^{INK4a}$, $p21^{CIP1}$ and *p53*), reduced DNA damage and H4K20me3 expression, as well as restored proliferation ability and metabolic balance in senescent NPCs, as validated through in vitro experiments. In a rat model of IVDD, OKS@M-Exo maintained intervertebral disc height, nucleus pulposus hydration and tissue structure, effectively ameliorated IVDD via decreasing the senescence markers. Additionally, OKS@M-Exo reduced nociceptive behavior and downregulated nociception markers, indicating its efficiency in alleviating LBP. The transcriptome sequencing analysis also demonstrated that OKS@M-Exo could decrease the expression of age-related pathways and restore cell proliferation. Collectively, reprogramming by the OKS@M-Exo to restore youthful epigenetics of senescent NPCs may hold promise as a therapeutic platform to treat IVDD.

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Optimal dietary patterns for healthy aging

As the global population ages, it is critical to identify diets that, beyond preventing noncommunicable diseases, optimally promote healthy aging. Here, using longitudinal questionnaire data from the Nurses' Health Study (1986–2016) and the Health Professionals Follow-Up Study (1986–2016), we examined the association of long-term adherence to eight dietary patterns and ultraprocessed food consumption with healthy aging, as assessed according to measures of cognitive, physical and mental health, as well as living to 70 years of age free of chronic diseases. After up to 30 years of follow-up, 9,771 (9.3%) of 105,015 participants (66% women, mean age = 53 years (s.d. = 8)) achieved healthy aging. For each dietary pattern, higher adherence was associated with greater odds of healthy aging and its domains. The odds ratios for the highest quintile versus the lowest ranged from 1.45 (95% confidence interval (CI) = 1.35–1.57; healthful plant-based diet) to 1.86 (95% CI = 1.71–2.01; Alternative Healthy Eating Index). When the age threshold for healthy aging was shifted to 75 years, the Alternative Healthy Eating Index diet showed the strongest association with healthy aging, with an odds ratio of 2.24 (95% CI = 2.01–2.50). Higher intakes of fruits, vegetables, whole grains, unsaturated fats, nuts, legumes and low-fat dairy products were linked to greater odds of healthy aging, whereas higher intakes of trans fats, sodium, sugary beverages and red or processed meats (or both) were inversely associated. Our findings suggest that dietary patterns rich in plant-based foods, with moderate inclusion of healthy animal-based foods, may enhance overall healthy aging, guiding future dietary guidelines.

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PREPRINT

Human brain cell-type-specific aging clocks based on single-nuclei transcriptomics

Aging is the primary risk factor for most neurodegenerative diseases, yet the cell-type-specific progression of brain aging remains poorly understood. Here, we developed human cell-type-specific transcriptomic aging clocks using high-quality single-nucleus RNA sequencing data from post mortem human prefrontal cortex tissue of 31 donors aged 18 – 94 years, encompassing 73,941 high-quality nuclei. We observed distinct transcriptomic changes across major cell types, including upregulation of inflammatory response genes in microglia from older samples. Aging clocks trained on each major cell type accurately predicted chronological age and remained robust in independent single-nucleus RNA-sequencing datasets, underscoring their broad applicability. These findings demonstrate the feasibility of cell-type-specific transcriptomic clocks to measure biological aging in the human brain and highlight potential mechanisms of selective vulnerability in neurodegenerative diseases. We anticipate these clocks will serve as a basis for further studies in other brain regions and more diverse populations, ultimately advancing our understanding of age-related neurodegenerative processes at the single-cell level.

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Young fibroblast-derived migrasomes alleviate keratinocyte senescence and enhance wound healing in aged skin

Background

Alterations in intercellular communication driven by cellular senescence constitute an important factor in skin aging. Migrasome, a newly discovered vesicular organelle, efficiently participates in intercellular communication; however, the relationship between cellular senescence and migrasomes remains unreported.

Objective

This study aims to explore the possible relationship between cellular senescence and migrasomes formation, and investigate the effects of young fibroblast-derived migrasomes on senescent keratinocytes and wound healing in aged skin.

Result

Single-cell RNA sequencing (scRNA-seq) data analysis revealed that fibroblasts exhibited the highest level of transcriptional variability during skin aging, and the degree of fibroblast senescence negatively correlated with the expression level of migrasome-associated markers. Further multiplex Immunohistochemistry (mIHC) results suggested that younger mouse skin contained more migrasomes than older mouse skin. Transmission electron microscopy (TEM) observations demonstrated abundant migrasomes in the skin from young individuals. In vitro experiments indicated that young fibroblasts produced significantly more migrasomes than senescent fibroblasts, as confirmed by wheat germ agglutinin (WGA) staining and scanning electron microscopy (SEM). Importantly, purified migrasomes from young fibroblasts were found to reduce the expression of senescence-associated markers in HaCaT cells. In vivo, using a wound healing model in naturally aged mice, we observed that migrasomes derived from young fibroblasts not only accelerated wound healing but also reduced senescence-associated marker expression in the skin.

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Rationale and design of the Dog Aging Project precision cohort: a multi-omic resource for longitudinal research in geroscience

A significant challenge in multi-omic geroscience research is the collection of high quality, fit-for-purpose biospecimens from a diverse and well-characterized study population with sufficient sample size to detect age-related changes in physiological biomarkers. The Dog Aging Project designed the precision cohort to study the mechanisms underlying age-related change in the metabolome, microbiome, and epigenome in companion dogs, an emerging model system for translational geroscience research. One thousand dog-owner pairs were recruited into cohort strata based on life stage, sex, size, and geography. We designed and built a novel implementation of the REDCap electronic data capture system to manage study participants, logistics, and biospecimen and survey data collection in a secure online platform. In collaboration with primary care veterinarians, we collected and processed blood, urine, fecal, and hair samples from 976 dogs. The resulting data include complete blood count, chemistry profile, immunophenotyping by flow cytometry, metabolite quantification, fecal microbiome characterization, epigenomic profile, urinalysis, and associated metadata characterizing sample conditions at collection and during lab processing. The project, which has already begun collecting second- and third-year samples from precision cohort dogs, demonstrates that scientifically useful biospecimens can be collected from a geographically dispersed population through collaboration with private veterinary clinics and downstream labs. The data collection infrastructure developed for the precision cohort can be leveraged for future studies. Most important, the Dog Aging Project is an open data project. We encourage researchers around the world to apply for data access and utilize this rich, constantly growing dataset in their own work.

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Impact of DNA-Methylation Age Acceleration on Long-Term Mortality Among US Adults With Cardiovascular-Kidney-Metabolic Syndrome

Background: The association between DNA methylation age acceleration (DNAmAA) and cardiovascular-kidney-metabolic (CKM) syndrome stages and long-term mortality in the population with CKM syndrome remains unclear.

Methods and results: This cohort study included 1889 participants from the National Health and Nutrition Examination Survey (1999-2002) with CKM stages and DNA methylation age data. DNAmAA was calculated as residuals from the regression of DNA methylation age on chronological age. The primary outcome was all-cause mortality, with cardiovascular and noncardiovascular mortality as secondary outcomes. Proportional odds models assessed the associations between DNAmAAs and CKM stages, and Cox proportional hazards regression models estimated the associations between DNAmAAs and mortality. Significant associations were found between DNAmAAs and advanced CKM stages, particularly for GrimAge2Mort acceleration (GrimAA) (odds ratio [OR], 1.547 [95% CI, 1.316-1.819]). Over an average follow-up of 14 years, 1015 deaths occurred. Each 5-unit increase in GrimAA was associated with a 50% increase in all-cause mortality (95% CI, 1.39-1.63), a 77% increase in cardiovascular mortality (95% CI, 1.46-2.15), and a 42% increase in noncardiovascular mortality (95% CI, 1.27-1.59). With the lowest GrimAA tertile as a reference, the highest GrimAA tertile showed hazard ratios of 1.95 (95% CI, 1.56-2.45) for all-cause mortality, 3.06 (95% CI, 2.13-4.40) for cardiovascular mortality, and 1.65 (95% CI, 1.20-2.29) for noncardiovascular mortality. Mediation analysis indicated that GrimAA mediates the association between various exposures (including physical activity, Healthy Eating Index-2015 score, hemoglobin A1c, etc.) and mortality.

Conclusions: GrimAA may serve as a valuable biomarker for assessing CKM stages and mortality risk in individuals with CKM syndrome, thereby informing personalized management strategies.

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Impact of Lipid-Lowering Combination Therapy With Statins and Ezetimibe vs Statin Monotherapy on the Reduction of Cardiovascular Outcomes: A Meta-analysis

Results

A total of 14 studies (11 randomized controlled trials and 3 cohort studies) with 108,373 very high-risk patients were included in the final analysis. The mean age of the patients in the combination LLT group and the statin monotherapy group was 67.31 and 67.89 years, respectively. Pooled analysis revealed that combination LLT significantly more effectively reduced the LDL-C level from baseline (mean difference, −12.96 mg/dL; 95% CI, −17.27 to −8.65; *P*<.001) and significantly reduced all-cause mortality (OR, 0.81; 95% CI, 0.67 to 0.97; *P*=.02), major adverse cardiovascular events (OR, 0.82; 95% CI, 0.69 to 0.97; *P*=.02), and stroke incidence (OR, 0.83; 95% CI, 0.75 to 0.91; *P*<.001), with an insignificant effect on cardiovascular mortality (OR, 0.86; 95% CI, 0.65 to 1.12; *P*=.26) when compared with statin monotherapy. The risk of adverse events and the therapy discontinuation rate were comparable between groups.

Conclusion

Combination LLT was associated with an overall greater reduction in LDL-C, the same risk of adverse effects, and significantly lower risk of all-cause mortality, major adverse cardiovascular events, and stroke compared with statin monotherapy. Forthcoming guidelines should consider the lipid-lowering combination therapy as early as possible, preferably up-front, for more effective LDL-C goal achievement and significant reduction of cardiovascular disease outcomes and mortality in high- and very high-risk patients.

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PREPRINT

Ketone Catabolism is Essential for Maintaining Normal Heart Function During Aging

The heart utilizes various nutrient sources for energy production, primarily favoring fatty acid oxidation. While ketones can be fuel substrates, ketolysis has been shown to be dispensable for heart development and function in mice. However, the long-term consequences of ketolysis downregulation in the heart remain unknown. Here we demonstrate that ketone catabolism is essential for preserving cardiac function during aging. The cardiac expression of succinyl-CoA:3-ketoacid CoA transferase (SCOT), a rate-limiting enzyme in ketolysis, decreases with aging in female mice. SCOT cardiomyocyte-specific knockout (cKO) mice exhibit normal heart function at 10 weeks of age but progressively develop cardiac dysfunction and remodeling as they age, without overt hypertrophy in both sexes. Notably, ketone supplementation via a ketogenic diet partially rescues contractile dysfunction in SCOT cKO mice, suggesting ketone oxidation-independent mechanisms contribute to the development of cardiomyopathy caused by SCOT downregulation. These findings indicate that ketone catabolism is crucial for maintaining heart function during aging, and that ketones confer cardioprotection independently of ketone oxidation.

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PREPRINT

Deficiency of mitophagy mediator Parkin in aortic smooth muscle cells exacerbates abdominal aortic aneurysm

Abdominal aortic aneurysms (AAAs) are a degenerative aortic disease and associated with hallmarks of aging, such as mitophagy. Despite this, the exact associations among mitophagy, aging, and AAA progression remain unknown. In our study, gene expression analysis of human AAA tissue revealed downregulation of mitophagy pathways, mitochondrial structure, and function-related proteins. Human proteomic analyses identified decreased levels of mitophagy mediators PINK1 and Parkin. Aged mice and, separately, a murine AAA model showed reduced mitophagy in aortic vascular smooth muscle cells (VSMCs) and PINK1 and Parkin expression. Parkin knockdown in VSMCs aggravated AAA dilation in murine models, with elevated mitochondrial ROS and impaired mitochondrial function. Importantly, inhibiting USP30, an antagonist of the PINK1/Parkin pathway, increased mitophagy in VSMCs, improved mitochondrial function, and reduced AAA incidence and growth. Our study elucidates a critical mechanism that proposes AAAs as an age-associated disease with altered mitophagy, introducing new potential therapeutic approaches.

Hemophilia is associated with accelerated biological aging

Marina Trappl [1], Rafaela Vostatek [1], Manuel Salzmann [2], Daniel Kraemmer [1], Johanna Gebhart [1], Philipp Hohensinner [3], Ingrid Pabinger [1], Cihan Ay [4]

Hemophilia is a rare X-linked bleeding disorder caused by mutations in the F8 or F9 gene (hemophilia A or B), leading to deficient factor VIII or IX proteins, respectively. Hemophilia-related complications caused by bleeding into the joints (the hallmark of hemophilia) and age-related comorbidities occur frequently and impact the functionality and quality of life of persons with hemophilia (PwH). Given the chronic nature of hemophilia, we hypothesized that hemophilia has an association with accelerated biological aging. Therefore, we investigated biological aging biomarkers, i.e. telomere length and mitochondrial DNA (mtDNA) copy number with a quantitative-PCR-based assay in PwH (n=99) and age- and sex-matched healthy controls (n=61). The association of telomere length and mtDNA copy number with hemophilia severity was investigated using ordinary-least-squares linear regression models allowing for interactions with chronological age. Telomere length (6.09 [4.79-7.68] kb vs. 10.07 [7.93-12.66] kb, p.

A torpor–like state in mice slows blood epigenetic aging and prolongs healthspan

Torpor and hibernation are extreme physiological adaptations of homeotherms associated with pro-longevity effects. Yet the underlying mechanisms of how torpor affects aging, and whether hypothermic and hypometabolic states can be induced to slow aging and increase healthspan, remain unknown. Here we demonstrate that the activity of a spatially defined neuronal population in the preoptic area, which has previously been identified as a torpor-regulating brain region, is sufficient to induce a torpor-like state (TLS) in mice. Prolonged induction of TLS slows epigenetic aging across multiple tissues and improves healthspan. We isolate the effects of decreased metabolic rate, long-term caloric restriction, and decreased core body temperature (T_b) on blood epigenetic aging and find that the decelerating effect of TLSs on aging is mediated by decreased T_b. Taken together, our findings provide novel mechanistic insight into the decelerating effects of torpor and hibernation on aging and support the growing body of evidence that T_b is an important mediator of the aging processes.

C. elegans aging research

A high precision method of segmenting complex postures in Caenorhabditis elegans and deep phenotyping to analyze lifespan

In-depth exploration of the effects of genes on the development, physiology, and behavior of organisms requires high-precision phenotypic analysis. However, the overlap of body postures in group behavior and the similarity of movement patterns between strains pose challenges to accuracy analysis. To address this issue, we designed the WormYOLO model based on the YOLO architecture, which improves the segmentation performance of C .elegans and effectively handles overlapping poses in images. In detection and segmentation tasks, WormYOLO performs well on the more overlapping Mating dataset, with its object detection performance improving by 24.1% ($mAP_{0.5:0.95}$) compared to Deep-worm-tracker, and its segmentation performance improving by 9.3% ($mAP_{0.5:0.95}$) compared to WormSwin. In addition, we propose a more accurate novel bending counting algorithm. In experiments, WormYOLO segmented images, followed by a feature point extraction algorithm to identify changes in worm skeleton positions, ultimately quantifying behavioral features with a counting algorithm. We conducted analytical experiments on various mutant strains based on their motion characteristics, investigating behavioral differences among the strains and assessing the correlation between high-dimensional phenotypic traits and relative lifespan.

Topoisomerase inhibitor amonafide enhances defense responses to promote longevity in C. elegans

Aging is a major risk factor for disease, and developing effective pharmaceutical interventions to improve healthspan and promote longevity has become a high priority for society. One of the molecular pathways related to longevity in various model organisms revolves around lowering AKT1 levels. This prompted our in silico drug screen for small molecules capable of mimicking the transcriptional effects of AKT1 knockdown. We found topoisomerase inhibitors as a top candidate longevity-drug class. Evaluating multiple compounds from this class in C. elegans revealed that the topoisomerase inhibitor amonafide has the greatest benefit on healthspan and lifespan. Intriguingly, the longevity effect of amonafide was not solely dependent on DAF-16/FOXO, the canonical pathway for lifespan extension via AKT1 inhibition. We performed RNA-seq on amonafide-treated worms and revealed a more youthful transcriptional signature, including the activation of diverse molecular and cellular defense pathways. We found the mitochondrial unfolded protein response (UPR^{mt}) regulator afts-1 to be crucial for both improved healthspan and extended lifespan upon amonafide treatment. Moreover, healthspan was partially dependent on the immune response transcription factor zip-2 and the integrated stress response transcription factor atf-4. We further examined the potential of amonafide in age-related disease. Treating a C. elegans model for Parkinson's disease with amonafide improved mobility. In conclusion, we identified amonafide as a novel geroprotector, which activates mitochondrial-, pathogen-, and xenobiotic-associated defense responses that-though more studies are needed-may serve as a candidate for Parkinson's disease therapy.

REVIEWS/COMMENTS/ METHODS/EDITORIALS

The ongoing challenge of slowing ageing through drug discovery

David G Le Couteur [1] [2], Stephen J Simpson [2], Victoria C Cogger [1], Janani Thillainadesan [1], Rozalyn Anderson [3], Rafael de Cabo [4]

What are the reasons for the repeated failures of clinical trials with anti-amyloid drugs for AD treatment?

Genetic, Socioecological, and Health Determinants of Extreme Longevity in Semi-Supercentenarians and Supercentenarians: Protocol for a Scoping Review

Methods: This scoping review follows the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) 2015 guidelines and the Population, Exposure, and Outcome framework. It includes observational and interventional, quantitative and qualitative studies on supercentenarians and semi-supercentenarians. Data will be sourced from databases like Scopus, PubMed, ProQuest, PsycINFO, and The Cochrane Library. The selection process involves abstract and full-text screening by two independent reviewers, with data extraction focusing on study characteristics, participant demographics, interventions or exposures, and key findings. A thematic analysis will identify patterns across various themes.

Results: As of October 2, 2024, five databases were searched, yielding 844 studies. After removing duplicates, 706 studies remained. Following the first and second screening stages, 135 studies were found to be eligible. The study is expected to be completed by the end of February 2025.

Conclusions: By synthesizing evidence, this study will understand the global scope of supercentenarians, describe the main themes of research interest, and identify gaps. The findings are expected to contribute significantly to the body of knowledge on longevity, informing future research and public health policies. This scoping review aims to enhance the understanding of factors promoting healthy aging and extreme longevity, benefiting broader public health initiatives.

Adrenal cortex senescence: an ageing-related pathology?

The adrenal glands are a pair of endocrine organs that produce and secrete mineralocorticoids, glucocorticoids, sex hormones, adrenaline, and noradrenaline. They have a vital role in a range of physiological processes including regulating electrolyte balance, blood pressure and metabolism, immunomodulation, sexual development and the stress response. Adrenal cortex senescence describes the ageing-related decline in the normal functioning of the adrenal cortex, characterised by an alteration in the output of adrenal cortical hormones, in particular reduced secretion of dehydroepiandrosterone (DHEA) and sulfated dehydroepiandrosterone (DHEAS). Such endocrine aberrations may be implicated in adverse clinical outcomes including mood disturbances, impairment in cognitive functioning, metabolic dysfunction and osteopenia. This paper shall address whether adrenal cortex senescence should be recognised as an ageing-related pathology, which has recently been defined as one that develops and/or progresses with increasing chronological age, that is associated with, or contributes to, functional decline, and is evidenced by studies in humans.

Metabolaging: a new geroscience perspective linking aging pathologies and metabolic dysfunction

With age, our metabolic systems undergo significant alterations, which can lead to a cascade of adverse effects that are implicated in both metabolic disorders, such as diabetes, and in the body's ability to respond to acute stress and trauma. To elucidate the metabolic imbalances arising from aging, we introduce the concept of "metabolaging." This framework encompasses the broad spectrum of metabolic disruptions associated with the hallmarks of aging, including the functional decline of key metabolically active organs, like the adipose tissue. By examining how these organs interact with essential nutrient-sensing pathways, "metabolaging" provides a more comprehensive view of the systemic metabolic imbalances that occur with age. This concept extends to understanding how age-related metabolic disturbances can influence the response to acute stressors, like burn injuries, highlighting the interplay between metabolic dysfunction and the ability to handle severe physiological challenges. Finally, we propose potential interventions that hold promise in mitigating the effects of metabolaging and its downstream consequences.

Mitochondria: An overview of their origin, genome, architecture, and dynamics

João P Moura [1], Paulo J Oliveira [2], Ana M Urbano [3]

Mitochondria are traditionally viewed as the powerhouses of eukaryotic cells, i.e., the main providers of the metabolic energy required to maintain their viability and function. However, the role of these ubiquitous intracellular organelles far extends energy generation, encompassing a large suite of functions, which they can adjust to changing physiological conditions. These functions rely on a sophisticated membrane system and complex molecular machineries, most of which imported from the cytosol through intricate transport systems. In turn, mitochondrial plasticity is rooted on mitochondrial biogenesis, mitophagy, fusion, fission, and movement. Dealing with all these aspects and terminology can be daunting for newcomers to the field of mitochondria, even for those with a background in biological sciences. The aim of the present educational article, which is part of a special issue entitled "Mitochondria in aging, cancer and cell death", is to present these organelles in a simple and concise way. Complex molecular mechanisms are deliberately omitted, as their inclusion would defeat the stated purpose of the article. Also, considering the wide scope of the article, coverage of each topic is necessarily limited, with the reader directed to excellent reviews, in which the different topics are discussed in greater depth than is possible here. In addition, the multiple cell type-specific genotypic and phenotypic differences between mitochondria are largely ignored, focusing instead on the characteristics shared by most of them, with an emphasis on mitochondria from higher eukaryotes. Also ignored are highly degenerate mitochondrion-related organelles, found in various anaerobic microbial eukaryotes lacking canonical mitochondria.

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Antiageing strategy for neurodegenerative diseases: from mechanisms to clinical advances

In the context of global ageing, the prevalence of neurodegenerative diseases and dementia, such as Alzheimer's disease (AD), is increasing. However, the current symptomatic and disease-modifying therapies have achieved limited benefits for neurodegenerative diseases in clinical settings. Halting the progress of neurodegeneration and cognitive decline or even improving impaired cognition and function are the clinically meaningful goals of treatments for neurodegenerative diseases. Ageing is the primary risk factor for neurodegenerative diseases and their associated comorbidities, such as vascular pathologies, in elderly individuals. Thus, we aim to elucidate the role of ageing in neurodegenerative diseases from the perspective of a complex system, in which the brain is the core and peripheral organs and tissues form a holistic network to support brain functions. During ageing, the progressive deterioration of the structure and function of the entire body hampers its active and adaptive responses to various stimuli, thereby rendering individuals more vulnerable to neurodegenerative diseases. Consequently, we propose that the prevention and treatment of neurodegenerative diseases should be grounded in holistic antiageing and rejuvenation means complemented by interventions targeting disease-specific pathogenic events. This integrated approach is a promising strategy to effectively prevent, pause or slow down the progression of neurodegenerative diseases.

Could immunotherapy and regulatory T cells be used therapeutically to slow the progression of Alzheimer's disease?

Alzheimer's disease and other cognitive impairments are a growing problem in the healthcare world with the ageing population. There are currently no effective treatments available; however, it has been suggested that targeting neuroinflammation may be a successful approach in slowing the progression of neurodegeneration. Reducing the destructive hyperinflammatory pathology to maintain homeostasis in neural tissue is a promising option to consider. This review explores the mechanisms behind neuroinflammation and the effectiveness of immunotherapy in slowing the progression of cognitive decline in patients with Alzheimer's disease. The key components of neuroinflammation in Alzheimer's disease researched are microglia, astrocytes, cytokines and CD8+ effector T cells. The role of oxidative stress on modulating regulatory T cells and some of the limitations of regulatory T cell-based therapies are also explored. Increasing regulatory T cells can decrease activation of microglia, proinflammatory cytokines and astrocytes; however, it can also increase levels of inflammatory cytokines. There is a complex network of regulatory T cell interactions that reduce Alzheimer's disease pathology, which is not fully understood. Exploring the current literature, further research into the use of immunotherapy in Alzheimer's disease is vital to determine the potential of these techniques; however, there is sufficient evidence to suggest that increasing regulatory T cells count does prevent Alzheimer's disease symptoms and pathology in patients with Alzheimer's disease. Some exciting innovative therapies are muted to explore in the future. The function of regulatory T cells in the presence of reactive oxygen species and oxidative stress should be investigated further in patients with neurogenerative disorders to ascertain if combination therapies could reduce oxidative stress while also enhancing regulatory T cells function. Could methods of immunotherapy infuse exogenous functional Tregs or enhance the immune environment in favour of endogenous regulatory T cells differentiation, thus reducing neuroinflammation in neurodegenerative pathology, inhibiting the progression of Alzheimer's disease?

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The Epigenetic Landscape: From Molecular Mechanisms to Biological Aging

Authors: Rachel Evangelina, Subhashree Ganesan, and Melvin George | AUTHORS INFO & AFFILIATIONS

Epigenetics, the study of heritable changes in gene expression that do not involve alterations to the deoxyribonucleic acid (DNA) sequence, plays a pivotal role in cellular function, development, and aging. This review explores key epigenetic mechanisms, including DNA methylation (DNAm), histone modifications, chromatin remodeling, RNA-based regulation, and long-distance chromosomal interactions. These modifications contribute to cellular differentiation and function, mediating the dynamic interplay between the genome and environmental factors. Epigenetic clocks, biomarkers based on DNAm patterns, have emerged as powerful tools to measure biological age and predict health span. This article highlights the evolution of epigenetic clocks, from first-generation models such as Horvath's multi-tissue clock to advanced second- and third-generation clocks such as DNAGrimAge and DunedinPACE, which incorporate biological parameters and clinical biomarkers for precise age estimation. Moreover, the role of epigenetics in aging and age-related diseases is discussed, emphasizing its impact on genomic stability, transcriptional regulation, and cellular senescence. Epigenetic dysregulation is implicated in cancer, genetic disorders, and neurodegenerative diseases, making it a promising target for therapeutic interventions. The reversibility of epigenetic modifications offers hope for mitigating age acceleration and enhancing health span through lifestyle changes and pharmacological approaches.

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Metabolic Signaling as a Driver of T Cell Aging

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Abstract

Aging significantly diminishes T cell immunity, increasing susceptibility to infections and reducing vaccine efficacy in older individuals. Metabolism plays a key role in T cell function, shaping their energy requirements, activation, and differentiation. Recent studies highlight altered metabolic signaling as a pivotal factor in T cell aging, influencing the ability of T cells to maintain quiescence, respond to activation, and differentiate into functional subsets. Aberrant metabolic pathways disrupt the quiescence of aged T cells and skew their differentiation toward short-lived, pro-inflammatory effector T cells while hindering the generation of long-lived memory and T follicular helper cells. These changes contribute to a hyper-inflammatory state, exacerbate chronic low-grade inflammation, and compromise immune homeostasis. In this review, we explore how metabolic signaling is altered during T cell aging and the resulting functional impacts. We also discuss therapeutic approaches aimed at restoring proper T cell differentiation, improving vaccine responses, and rejuvenating immune function in older populations.

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How to promote healthy aging across the life cycle

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The global rise in aging populations is challenging healthcare systems, especially in developed countries. Despite advancements in healthcare and living standards, the extension of lifespan has not been matched by an equivalent improvement in healthspan, leading to a higher prevalence of chronic diseases and disabilities in older adults. This review examines strategies to promote healthy aging throughout the life cycle, emphasizing the importance of a comprehensive strategy that integrates individual, healthcare, and environmental approaches.

Individual strategies include lifestyle factors like diet, physical activity, and social connections. Healthcare approaches focus on improving health literacy, vaccinations, and screenings. Environmental approaches aim to mitigate climate change, reduce pollution, and design longevity-ready cities. A comprehensive strategy combining individual approaches, public health measures, innovative policies, and community support is essential for helping populations live longer, healthier, and more independent lives. Looking forward, this will be complemented by personalized approaches, focusing on individual traits and biological backgrounds. The key to this lies in geroscience, which studies the biological and molecular mechanisms of aging and how they contribute to age-related diseases and functional decline, aiming to design targeted interventions to slow aging and improve quality of life. Artificial intelligence will play a key role in analyzing these complex factors and creating innovative solutions.

In conclusion, aging is shaped by various factors, requiring more than one solution. A combination of comprehensive and personalized strategies can bridge the gap between public health measures and personalized care, offering the scientific insights needed to slow aging and enhance quality of life.

Strategies for studying sex differences in brain aging

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Studying sex effects and their underlying mechanisms is of major relevance to understanding brain health. Despite growing interests, experimentally studying sex differences, particularly in the context of aging, remains challenging. Since sex chromosomal content influences gonadal development, separating the effects of gonadal hormones and chromosomal factors requires specific model systems. Here, we highlight rodent and tractable models for examining sex dimorphism in brain and cognitive aging. In addition, we discuss multi-omic and bioinformatic approaches that yield biological insights from animal and human studies. This review provides a comprehensive overview of the diverse toolkit now available to advance our understanding of sex differences in brain aging.

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The complex interplay between aging and cancer

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Cancer is an age-related disease, but the interplay between cancer and aging is complex and their shared molecular drivers are deeply intertwined. This Review provides an overview of how different biological pathways affect cancer and aging, leveraging evidence mainly derived from animal studies. We discuss how genome maintenance and accumulation of DNA mutations affect tumorigenesis and tissue homeostasis during aging. We describe how age-related telomere dysfunction and cellular senescence intricately modulate tumor development through mechanisms involving genomic instability and inflammation. We examine how an aged immune system and chronic inflammation shape tumor immunosurveillance, fueling DNA damage and cellular senescence. Finally, as animal models are important to untangling the relative contributions of these aging-modulated pathways to cancer progression and to test interventions, we discuss some of the limitations of physiological and accelerated aging models, aiming to improve experimental designs and enhance translation.

Pluripotent stem cell-derived mesenchymal stem cells for therapeutic applications, developmental study, and cancer research

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Human mesenchymal stem cells (MSCs) have been widely studied and applied for the treatment of various diseases due to their crucial role in tissue repair and regeneration. Compared to MSCs isolated from somatic tissues, MSCs differentiated from human pluripotent stem cells (ps-MSCs) have demonstrated similar therapeutic effects while possessing some advantages in quality control and assurance, given their unlimited and consistent supply of source cells. This makes ps-MSCs highly druggable and promising for therapeutic applications. In this minireview, we introduce the latest progress in ps-MSC research, focusing on the therapeutic properties, origin, in vivo development, and application of ps-MSCs in cancer research. We will also discuss the perspectives and challenges of this relatively new source of MSCs.

OTHER RESEARCH & REVIEWS

A systems-level, semi-quantitative landscape of metabolic flux in C. elegans

Metabolic flux, or the rate of metabolic reactions, is one of the most fundamental metrics describing the status of metabolism in living organisms. However, measuring fluxes across the entire metabolic network remains nearly impossible, especially in multicellular organisms. Computational methods based on flux balance analysis have been used with genome-scale metabolic network models to predict network-level flux wiring[1-6]. However, such approaches have limited power because of the lack of experimental constraints. Here, we introduce a strategy that infers whole-animal metabolic flux wiring from transcriptional phenotypes in the nematode Caenorhabditis elegans. Using a large-scale Worm Perturb-Seq (WPS) dataset for roughly 900 metabolic genes[7], we show that the transcriptional response to metabolic gene perturbations can be integrated with the metabolic network model to infer a highly constrained, semi-quantitative flux distribution. We discover several features of adult C. elegans metabolism, including cyclic flux through the pentose phosphate pathway, lack of de novo purine synthesis flux and the primary use of amino acids and bacterial RNA as a tricarboxylic acid cycle carbon source, all of which we validate by stable isotope tracing. Our strategy for inferring metabolic wiring based on transcriptional phenotypes should be applicable to a variety of systems, including human cells.

Systems-level design principles of metabolic rewiring in an animal

The regulation of metabolism is vital to any organism and can be achieved by transcriptionally activating or repressing metabolic genes[1-3]. Although many examples of transcriptional metabolic rewiring have been reported[4], a systems-level study of how metabolism is rewired in response to metabolic perturbations is lacking in any animal. Here we apply Worm Perturb-Seq (WPS)-a high-throughput method combining whole-animal RNA-interference and RNA-sequencing[5]-to around 900 metabolic genes in the nematode Caenorhabditis elegans. We derive a metabolic gene regulatory network (mGRN) in which 385 perturbations are connected to 9,414 genes by more than 110,000 interactions. The mGRN has a highly modular structure in which 22 perturbation clusters connect to 44 gene expression programs. The mGRN reveals different modes of transcriptional rewiring from simple reaction and pathway compensation to rerouting and more complex network coordination. Using metabolic network modelling, we identify a design principle of transcriptional rewiring that we name the compensation-repression (CR) model. The CR model explains most transcriptional responses in metabolic genes and reveals a high level of compensation and repression in five core metabolic functions related to energy and biomass. We provide preliminary evidence that the CR model may also explain transcriptional metabolic rewiring in human cells.

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Implantation of engineered adipocytes suppresses tumor progression in cancer models

Tumors exhibit an increased ability to obtain and metabolize nutrients. Here, we implant engineered adipocytes that outcompete tumors for nutrients and show that they can substantially reduce cancer progression, a technology termed adipose manipulation transplantation (AMT). Adipocytes engineered to use increased amounts of glucose and fatty acids by upregulating *UCP1* were placed alongside cancer cells or xenografts, leading to significant cancer suppression. Transplanting modulated adipose organoids in pancreatic or breast cancer genetic mouse models suppressed their growth and decreased angiogenesis and hypoxia. Co-culturing patient-derived engineered adipocytes with tumor organoids from dissected human breast cancers significantly suppressed cancer progression and proliferation. In addition, cancer growth was impaired by inducing engineered adipose organoids to outcompete tumors using tetracycline or placing them in an integrated cell-scaffold delivery platform and implanting them next to the tumor. Finally, we show that upregulating *UPP1* in adipose organoids can outcompete a uridine-dependent pancreatic ductal adenocarcinoma for uridine and suppress its growth, demonstrating the potential customization of AMT.