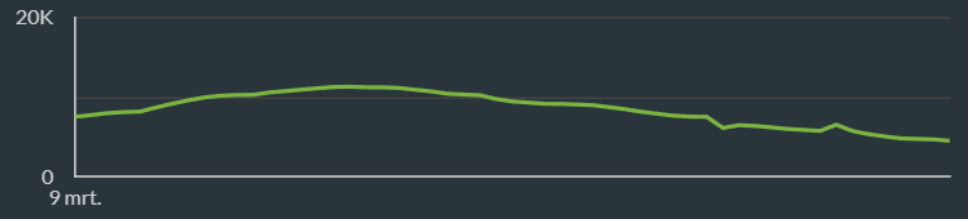
Heales
HEALTHY LIFE EXTENSION SOCIETY

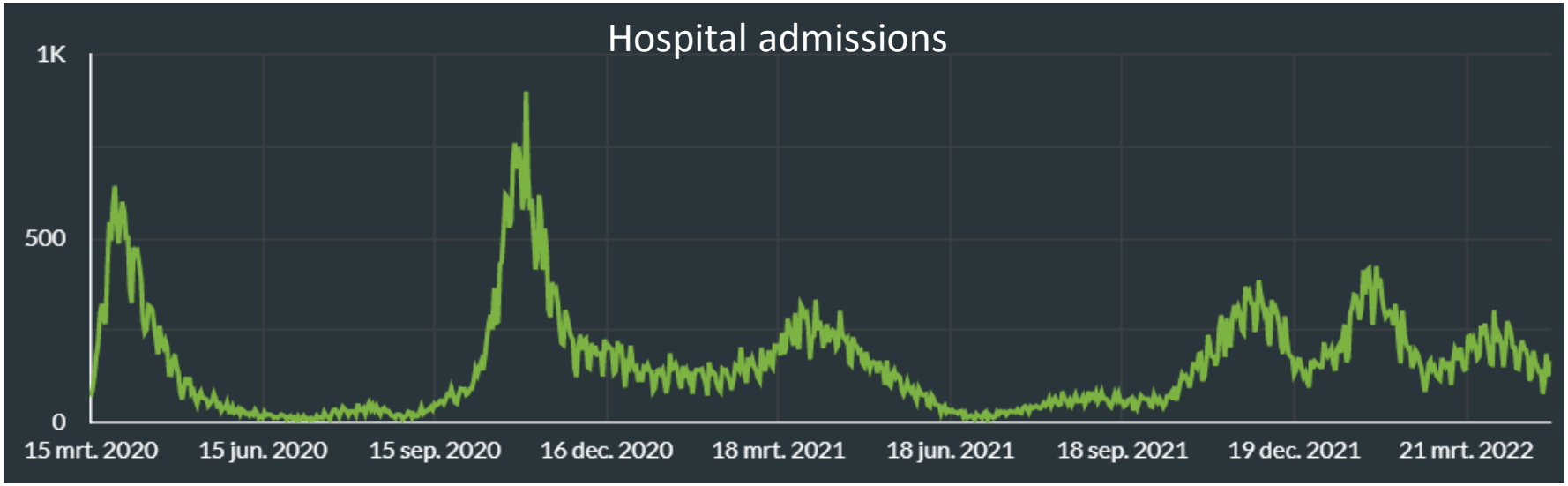
Scientific News
8th of May 2022
Sven Bulterijs

Business/Conferences/ General news

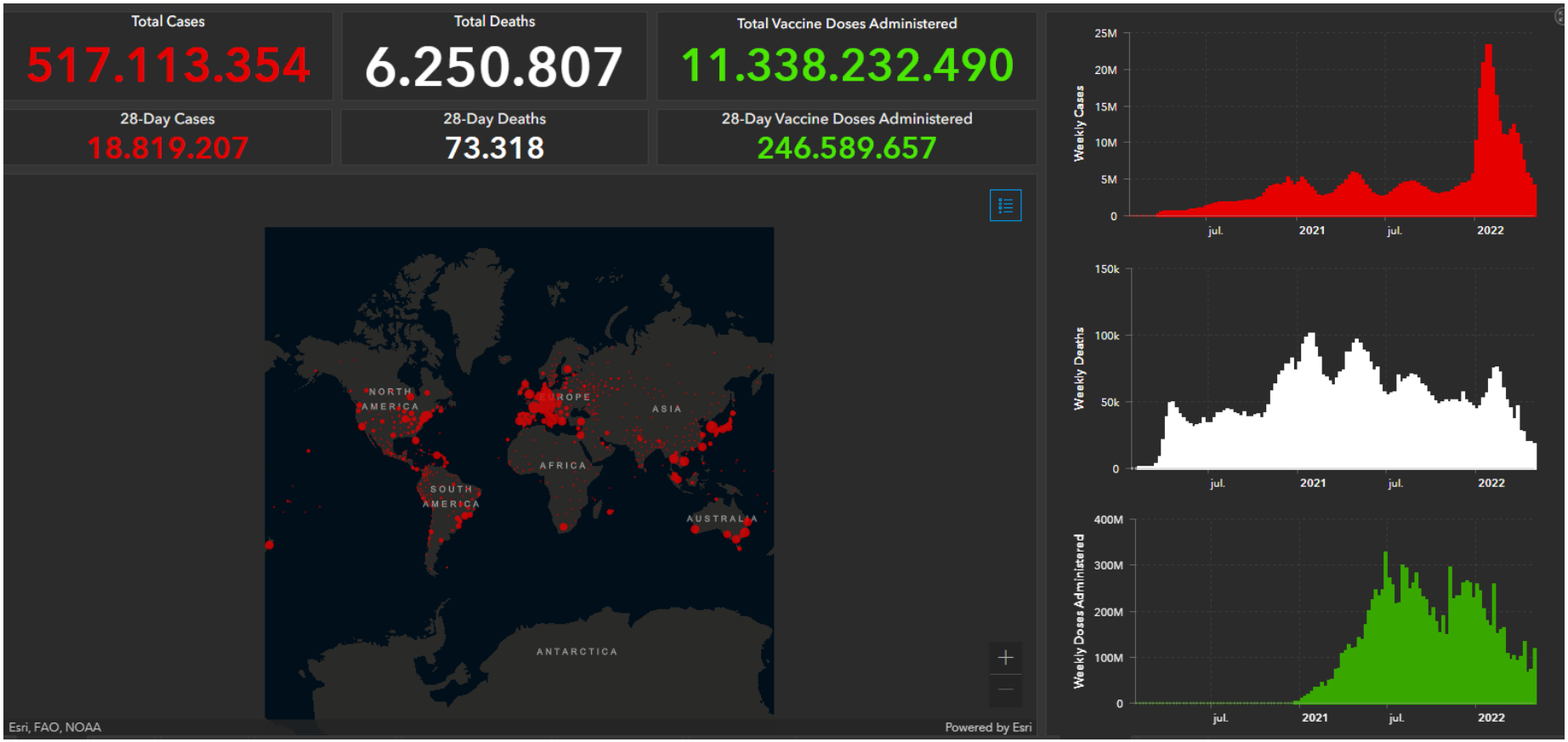
Belgium

	Total	Last 7 days Daily Average
Cases	4,1 mln.	4.483 * -31%





World



Heales
HEALTHY LIFE EXTENSION SOCIETY

15 million people have died in the pandemic, WHO says

The World Health Organization's long-awaited estimate of excess COVID deaths is in line with other studies.

David Adam

Crematorium workers in Delhi transport the body of a person who died from COVID-19. Credit: Anindito Mukherjee/Getty

Heales
HEALTHY LIFE EXTENSION SOCIETY

Why the WHO took two years to say COVID is airborne

Early in the pandemic, the World Health Organization stated that SARS-CoV-2 was not transmitted through the air. That mistake and the prolonged process of correcting it sowed confusion and raises questions about what will happen in the next pandemic.

Dyani Lewis

Accelerated biological aging in COVID-19 patients

Xue Cao, Wenjuan Li, Ting Wang, Dongzhi Ran, Veronica Davalos, Laura Planas-Serra, Aurora Pujol, Manel Esteller, Xiaolin Wang & Huichuan Yu

Nature Communications **13**, Article number: 2135 (2022) | Cite this article

27k Accesses | **896** Altmetric | Metrics

Abstract

Chronological age is a risk factor for SARS-CoV-2 infection and severe COVID-19. Previous findings indicate that epigenetic age could be altered in viral infection. However, the epigenetic aging in COVID-19 has not been well studied. In this study, DNA methylation of the blood samples from 232 healthy individuals and 413 COVID-19 patients is profiled using EPIC methylation array. Epigenetic ages of each individual are determined by applying epigenetic clocks and telomere length estimator to the methylation profile of the individual. Epigenetic age acceleration is calculated and compared between groups. We observe strong correlations between the epigenetic clocks and individual's chronological age ($r > 0.8$, $p < 0.0001$). We also find the increasing acceleration of epigenetic aging and telomere attrition in the sequential blood samples from healthy individuals and infected patients developing non-severe and severe COVID-19. In addition, the longitudinal DNA methylation profiling analysis find that the accumulation of epigenetic aging from COVID-19 syndrome could be partly reversed at late clinic phases in some patients. In conclusion, accelerated epigenetic aging is associated with the risk of SARS-CoV-2 infection and developing severe COVID-19. In addition, the accumulation of epigenetic aging from COVID-19 may contribute to the post-COVID-19 syndrome among survivors.

© REUTERS

Belgisch bedrijf ontwikkelt mRNA-vaccin dat tegen coronavarianten lijkt te beschermen

Een Belgisch bedrijf werkt aan een nieuw type mRNA-vaccin dat tegen varianten van het coronavirus lijkt te beschermen. De cellulaire immuunrespons die het 'saRNA'-vaccin uitlokt is beter getraind om infecties aan te vallen. Dat blijkt uit proeven op dieren, die hoopgevende resultaten hebben opgeleverd. Het is nog niet duidelijk wanneer de Belgische concurrent voor de bestaande mRNA-vaccins (Pfizer-BioNTech en Moderna) op de markt zal komen.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Kane Tanaka, the world's oldest person, dies at 119

Catherine Garcia, Night editor

April 26, 2022 · 1 min read

In this article:

Mother's Day

Kane Tanaka
Japanese supercent...

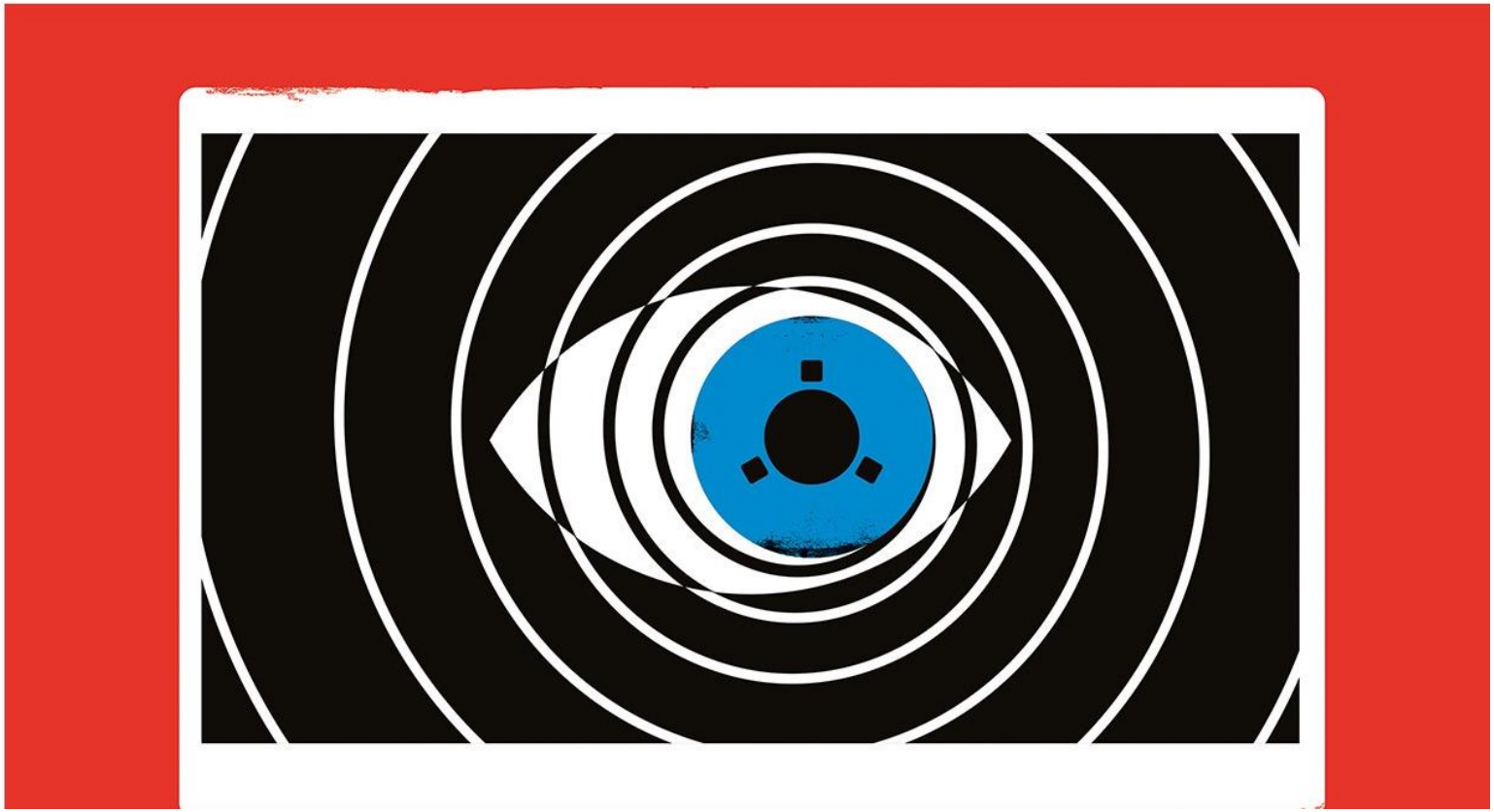
Kane Tanaka in 2019. The Asahi Shimbun via Getty Images

Heales
HEALTHY LIFE EXTENSION SOCIETY

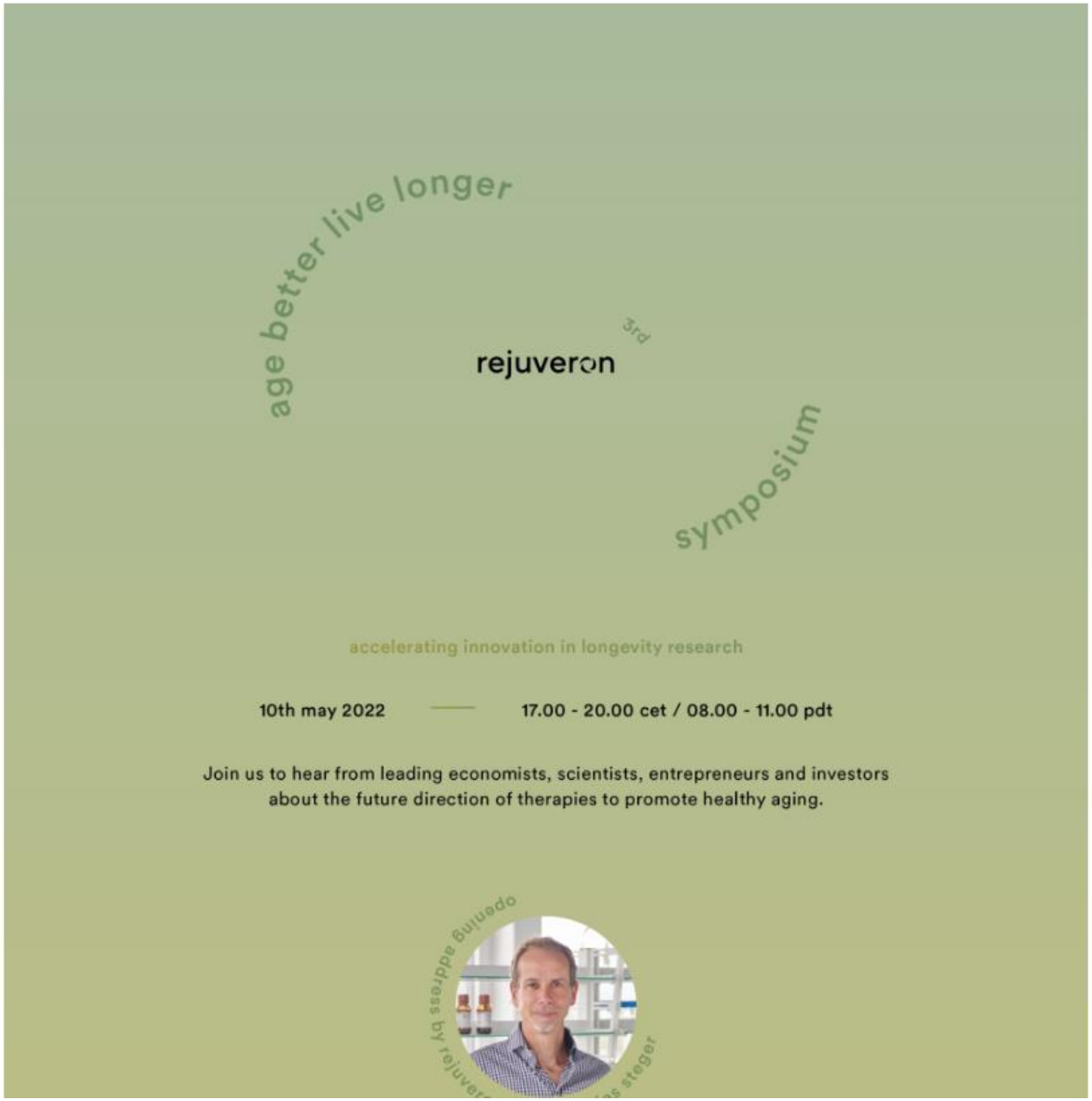
In pursuit of data immortality

Data sharing can save important scientific work from extinction, but only if researchers take care to ensure that resources are easy to find and reuse.

Michael Eisenstein



Rejuveron Age Better Live Longer Symposium



Heales
HEALTHY LIFE EXTENSION SOCIETY

ARDD 2022

THE 9th AGING RESEARCH & DRUG DISCOVERY MEETING

29 AUGUST — 2 SEPTEMBER

Aging research articles

Heales
HEALTHY LIFE EXTENSION SOCIETY

Somatic mutation rates scale with lifespan across mammals

Alex Cagan, Adrian Baez-Ortega, ... Iñigo Martincorena + Show authors

Nature **604**, 517–524 (2022) | Cite this article

102k Accesses | **1** Citations | **1486** Altmetric | Metrics

Abstract

The rates and patterns of somatic mutation in normal tissues are largely unknown outside of humans[1,2,3,4,5,6,7]. Comparative analyses can shed light on the diversity of mutagenesis across species, and on long-standing hypotheses about the evolution of somatic mutation rates and their role in cancer and ageing. Here we performed whole-genome sequencing of 208 intestinal crypts from 56 individuals to study the landscape of somatic mutation across 16 mammalian species. We found that somatic mutagenesis was dominated by seemingly endogenous mutational processes in all species, including 5-methylcytosine deamination and oxidative damage. With some differences, mutational signatures in other species resembled those described in humans[8], although the relative contribution of each signature varied across species. Notably, the somatic mutation rate per year varied greatly across species and exhibited a strong inverse relationship with species lifespan, with no other life-history trait studied showing a comparable association. Despite widely different life histories among the species we examined—including variation of around 30-fold in lifespan and around 40,000-fold in body mass—the somatic mutation burden at the end of lifespan varied only by a factor of around 3. These data unveil common mutational processes across mammals, and suggest that somatic mutation rates are evolutionarily constrained and may be a contributing factor in ageing.

Different responses to DNA damage determine ageing differences between organs

Organs age differently, causing wide heterogeneity in multimorbidity, but underlying mechanisms are largely elusive. To investigate the basis of organ-specific ageing, we utilized progeroid repair-deficient *Ercc1*$^{\Delta/-}$ mouse mutants and systematically compared at the tissue, stem cell and organoid level two organs representing ageing extremes. *Ercc1*$^{\Delta/-}$ intestine shows hardly any accelerated ageing. Nevertheless, we found apoptosis and reduced numbers of intestinal stem cells (ISCs), but cell loss appears compensated by over-proliferation. ISCs retain their organoid-forming capacity, but organoids perform poorly in culture, compared with WT. Conversely, liver ages dramatically, even causing early death in *Ercc1*-KO mice. Apoptosis, p21, polyploidization and proliferation of various (stem) cells were prominently elevated in *Ercc1*$^{\Delta/-}$ liver and stem cell populations were either largely unaffected (Sox9+), or expanding (Lgr5+), but were functionally exhausted in organoid formation and development *in vitro*. Paradoxically, while intestine displays less ageing, repair in WT ISCs appears inferior to liver as shown by enhanced sensitivity to various DNA-damaging agents, and lower lesion removal. Our findings reveal organ-specific anti-ageing strategies. Intestine, with short lifespan limiting time for damage accumulation and repair, favours apoptosis of damaged cells relying on ISC plasticity. Liver with low renewal rates depends more on repair pathways specifically protecting the transcribed compartment of the genome to promote sustained functionality and cell preservation. As shown before, the hematopoietic system with intermediate self-renewal mainly invokes replication-linked mechanisms, apoptosis and senescence. Hence, organs employ different genome maintenance strategies, explaining heterogeneity in organ ageing and the segmental nature of DNA-repair-deficient progerias.

Heales
HEALTHY LIFE EXTENSION SOCIETY

The burden of rare protein-truncating genetic variants on human lifespan

Jimmy Z. Liu, Chia-Yen Chen, Ellen A. Tsai, Christopher D. Whelan, David Sexton, Sally John & Heiko Runz

Nature Aging **2**, 289–294 (2022) | Cite this article

Abstract

Genetic predisposition has been shown to contribute substantially to the age at which we die. Genome-wide association studies (GWASs) have linked more than 20 loci to phenotypes related to human lifespan[1]. However, little is known about how lifespan is impacted by gene loss of function. Through whole-exome sequencing of 352,338 UK Biobank participants of European ancestry, we assessed the relevance of protein-truncating variant (PTV) gene burden on individual and parental survival. We identified four exome-wide significant ($P < 4.2 \times 10^{-7}$) human lifespan genes, *BRCA1*, *BRCA2*, *ATM* and *TET2*. Gene and gene-set, PTV-burden, phenome-wide association studies support known roles of these genes in cancer to impact lifespan at the population level. The *TET2* PTV burden was associated with a lifespan through somatic mutation events presumably due to clonal hematopoiesis. The overlap between PTV burden and common variant-based lifespan GWASs was modest, underscoring the value of exome sequencing in well-powered biobank cohorts to complement GWASs for identifying genes underlying complex traits.

Heales
HEALTHY LIFE EXTENSION SOCIETY

ETS1 acts as a regulator of human healthy aging via decreasing ribosomal activity

Adaptation to reduced energy production during aging is a fundamental issue for maintaining healthspan or prolonging life span. Currently, however, the underlying mechanism in long-lived people remains poorly understood. Here, we analyzed transcriptomes of 193 long-lived individuals (LLIs) and 86 spouses of their children from two independent Chinese longevity cohorts and found that the ribosome pathway was significantly down-regulated in LLIs. We found that the down-regulation is likely controlled by *ETS1* (ETS proto-oncogene 1), a transcription factor down-regulated in LLIs and positively coexpressed with most ribosomal protein genes (RPGs). Functional assays showed that ETS1 can bind to RPG promoters, while *ETS1* knockdown reduces RPG expression and alleviates cellular senescence in human dermal fibroblast (HDF) and embryonic lung fibroblast (IMR-90) cells. As protein synthesis/turnover in ribosomes is an energy-intensive cellular process, the decline in ribosomal biogenesis governed by *ETS1* in certain female LLIs may serve as an alternative mechanism to achieve energy-saving and healthy aging.

Heales
HEALTHY LIFE EXTENSION SOCIETY

FGF21 is required for protein restriction to extend lifespan and improve metabolic health in male mice

Cristal M. Hill ✉, Diana C. Albarado, Lucia G. Coco, Redin A. Spann, Md Shahjalal Khan, Emily Qualls-Creekmore, David H. Burk, Susan J. Burke, J. Jason Collier, Sangho Yu, David H. McDougal, Hans-Rudolf Berthoud, Heike Münzberg, Andrzej Bartke & Christopher D. Morrison ✉

Dietary protein restriction is increasingly recognized as a unique approach to improve metabolic health, and there is increasing interest in the mechanisms underlying this beneficial effect. Recent work indicates that the hormone FGF21 mediates the metabolic effects of protein restriction in young mice. Here we demonstrate that protein restriction increases lifespan, reduces frailty, lowers body weight and adiposity, improves physical performance, improves glucose tolerance, and alters various metabolic markers within the serum, liver, and adipose tissue of wildtype male mice. Conversely, mice lacking FGF21 fail to exhibit metabolic responses to protein restriction in early life, and in later life exhibit early onset of age-related weight loss, reduced physical performance, increased frailty, and reduced lifespan. These data demonstrate that protein restriction in aging male mice exerts marked beneficial effects on lifespan and metabolic health and that a single metabolic hormone, FGF21, is essential for the anti-aging effect of this dietary intervention.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Combining Stem Cell Rejuvenation and Senescence Targeting to Synergistically Extend Lifespan

Prameet Kaur, Agimaa Otgonbaatar, Anupriya Ramamoorthy, Ellora Hui Zhen Chua, Nathan Harmston, Jan Gruber, Nicholas S. Tolwinski

doi: https://doi.org/10.1101/2022.04.21.488994

ABSTRACT

Why biological age is a major risk factor for many of the most important human diseases remains mysterious. We know that as organisms age, stem cell pools are exhausted while senescent cells progressively accumulate. Independently, induction of pluripotency *via* expression of Yamanaka factors (*Oct4, Klf4, Sox2, c-Myc;* OKSM) and clearance of senescent cells have each been shown to ameliorate cellular and physiological aspects of aging, suggesting that both processes are drivers of organismal aging. However, stem cell exhaustion and cellular senescence likely interact in the etiology and progression of age-dependent diseases because both undermine tissue and organ homeostasis in different if not complementary ways. Here, we combine transient cellular reprogramming (stem cell rejuvenation) with targeted removal of senescent cells to test the hypothesis that simultaneously targeting both cell-fate based aging mechanisms will maximize life and health span benefits. We show that these interventions protect the intestinal stem cell pool, lower inflammation, activate pro-stem cell signaling pathways, and synergistically improve health and lifespan. Our findings suggest that a combination therapy, simultaneously replacing lost stem cells and removing senescent cells, shows synergistic potential for anti-aging treatments. Our finding that transient expression of both is the most effective suggests that drug-based treatments in non-genetically tractable organisms will likely be the most translatable.

Heales
HEALTHY LIFE EXTENSION SOCIETY

In vivo partial cellular reprogramming enhances liver plasticity and regeneration

Tomoaki Hishida [15] • Mako Yamamoto [15] • Yuriko Hishida-Nozaki • ... Pradeep Reddy • Guang-Hui Liu • Juan Carlos Izpisua Belmonte [16] • Show all authors • Show footnotes

Mammals have limited regenerative capacity, whereas some vertebrates, like fish and salamanders, are able to regenerate their organs efficiently. The regeneration in these species depends on cell dedifferentiation followed by proliferation. We generate a mouse model that enables the inducible expression of the four Yamanaka factors (Oct-3/4, Sox2, Klf4, and c-Myc, or 4F) specifically in hepatocytes. Transient *in vivo* 4F expression induces partial reprogramming of adult hepatocytes to a progenitor state and concomitantly increases cell proliferation. This is indicated by reduced expression of differentiated hepatic-lineage markers, an increase in markers of proliferation and chromatin modifiers, global changes in DNA accessibility, and an acquisition of liver stem and progenitor cell markers. Functionally, short-term expression of 4F enhances liver regenerative capacity through topoisomerase2-mediated partial reprogramming. Our results reveal that liver-specific 4F expression *in vivo* induces cellular plasticity and counteracts liver failure, suggesting that partial reprogramming may represent an avenue for enhancing tissue regeneration.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Deciphering the roadmap of *in vivo* reprogramming towards pluripotency

Dafni Chondronasiou, Jaime Martínez de Villareal, Elena Melendez, Cian J. Lynch, Marta Kovatcheva, Mònica Aguilera, Neus Prats, Francisco X. Real, Manuel Serrano

Differentiated cells can be converted to pluripotent stem cells (iPSCs) upon ectopic expression of transcription factors OCT4, SOX2, KLF4 and MYC (OSKM) in a process known as reprogramming. Great efforts have been made to dissect intermediate states of *in vitro* reprogramming and how they are affected by culture conditions, while the roadmap of *in vivo* reprogramming remains unexplored. Here, we use single cell RNA sequencing to capture cells undergoing reprogramming in the adult pancreas. We identify markers along the trajectory from acinar identity to pluripotency, which allow *in situ* visualization of the intermediate states of reprogramming. Importantly, different tissues expressing OSKM, such as pancreas, stomach and colon, share markers of intermediate reprogramming, suggesting a conserved *in vivo* reprogramming path. Our *in vivo* roadmap defines landmarks along *in vivo* reprogramming that could be useful for applications in tissue regeneration and cellular rejuvenation based on intermediate reprogramming states.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Natural killer cells act as an extrinsic barrier for in vivo reprogramming

Elena Melendez [1], Dafni Chondronasiou [1], Lluc Mosteiro [2], Jaime Martínez de Villarreal [3 4], Marcos Fernández-Alfara [1], Cian J Lynch [1], Dirk Grimm [5 6 7], Francisco X Real [3 4 8], José Alcamí [9 10 11], Núria Climent [9 10 12], Federico Pietrocola [1 13], Manuel Serrano [1 14]

Affiliations + expand

PMID: 35420133 DOI: 10.1242/dev.200361

Abstract

The ectopic expression of the transcription factors OCT4, SOX2, KLF4 and MYC (OSKM) enables reprogramming of differentiated cells into pluripotent embryonic stem cells. Methods based on partial and reversible in vivo reprogramming are a promising strategy for tissue regeneration and rejuvenation. However, little is known about the barriers that impair reprogramming in an in vivo context. We report that natural killer (NK) cells significantly limit reprogramming, both in vitro and in vivo. Cells and tissues in the intermediate states of reprogramming upregulate the expression of NK-activating ligands, such as MULT1 and ICAM1. NK cells recognize and kill partially reprogrammed cells in a degranulation-dependent manner. Importantly, in vivo partial reprogramming is strongly reduced by adoptive transfer of NK cells, whereas it is significantly increased by their depletion. Notably, in the absence of NK cells, the pancreatic organoids derived from OSKM-expressing mice are remarkably large, suggesting that ablating NK surveillance favours the acquisition of progenitor-like properties. We conclude that NK cells pose an important barrier for in vivo reprogramming, and speculate that this concept may apply to other contexts of transient cellular plasticity.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Combining adoptive NK cell infusion with a dopamine-releasing peptide reduces senescent cells in aged mice

Zongke Bai, Peiwei Yang, Fan Yu, Zhong Li, Zheng Yao, Jean Martinez, Mengwei Li & Hanmei Xu

Cell Death & Disease **13**, Article number: 305 (2022) | Cite this article

Abstract

Aging inducing the development of senescent cells (SNCs) in various tissues is considered as the main cause of the age-related diseases. Senotherapy has become a promising anti-aging therapy. However, the effectivity and side-effect of senolytic agents are still concern. Here, we observed the downregulation of senescence-related genes by adoptive infusion of natural killer (NK) cells in 26 cases in peripheral blood $CD3^+$ T cells. NK cell treatment also significantly decreased levels of senescence markers and senescence-associated secretory phenotypes (SASPs) in three senescent adipose tissues when culturing them together. Interestingly, cytotoxic activity of mouse NK cells against SNCs was significantly enhanced by dopamine in vitro through D1-like receptors. Acein, dopamine-releasing peptide, promoted the adoptive infusion of NK cells in effectively eliminating SNCs in a variety of tissues and reduced local and systemic SASPs in aging mice but Acein alone did not have the senolytic effect. These data demonstrated that adoptive infusion of NK cells is an effective means in removing SNCs, and peptide Acein combined with NK cells further enhances this effect in aging mice.

Once-daily feeding is associated with better health in companion dogs: results from the Dog Aging Project

Emily E Bray [1] [2], Zihan Zheng [3], M Katherine Tolbert [4], Brianah M McCoy [5], Dog Aging Project Consortium; Matt Kaeberlein [6], Kathleen F Kerr [3]

A variety of diets have been studied for possible anti-aging effects. In particular, studies of intermittent fasting and time-restricted feeding in laboratory rodents have found evidence of beneficial health outcomes. Companion dogs represent a unique opportunity to study diet in a large mammal that shares human environments. The Dog Aging Project has been collecting data on thousands of companion dogs of all different ages, sizes, and breeds since 2019. We leveraged this diverse cross-sectional dataset to investigate associations between feeding frequency and cognitive function (n = 10,474) as well as nine broad categories of health conditions (n = 24,238). Controlling for sex, age, breed, and other potential confounders, we found that dogs fed once daily rather than more frequently had lower mean scores on a cognitive dysfunction scale, and lower odds of having gastrointestinal, dental, orthopedic, kidney/urinary, and liver/pancreas disorders. Therefore, we find that once-daily feeding is associated with better health in multiple domains. Future research with longitudinal data can provide stronger evidence for a possible causal effect of feeding frequency on health in companion dogs.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Dog Size and Patterns of Disease History Across the Canine Age Spectrum: Results from the Dog Aging Project

Age in dogs is associated with the risk of many diseases, and canine size is a major factor in that risk. However, the size effect is not as simple as the age effect. While small size dogs tend to live longer, some diseases are more prevalent among small dogs. Utilizing owner-reported data on disease history from a substantial number of companion dogs, we investigate how body size, as measured by weight, associates with the prevalence of a reported condition and its pattern across age for various disease categories. We found significant positive associations between weight and prevalence of skin, bone/orthopedic, gastrointestinal, ear/nose/throat, cancer/tumor, brain/neurologic, endocrine, and infectious diseases. Similarly, weight was negatively associated with the prevalence of eye, cardiac, liver/pancreas, and respiratory disease categories. Kidney/urinary disease prevalence did not vary by weight. We also found that the association between age and disease prevalence varied by dog size for many conditions including eye, cardiac, orthopedic, ear/nose/throat, and cancer. Controlling for sex, purebred/mixed breed, and geographic region made little difference in all disease categories we studied. Our results align with the reduced lifespan in larger dogs for most of the disease categories but suggest potential avenues for further examination.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Evaluation of Cognitive Function in the Dog Aging Project: Associations with Baseline Canine Characteristics

Canine Cognitive Dysfunction (CCD) is a neurodegenerative disease in aging dogs. It has been described previously in relatively small cohorts of dogs using multiple different rating scales. This study aimed to use a minimally modified CCD rating scale developed by previous researchers to describe the prevalence of CCD more thoroughly in a large, nationwide cohort of companion dogs participating in the Dog Aging Project (DAP). Associations between various canine characteristics, predicted lifespan quartiles, and CCD were examined using univariable and multivariable logistic regression models and Receiver Operating Curve (ROC) analysis.

When controlling for all other characteristics, the odds of CCD increased 52% with each additional year of age. Among dogs of the same age, health status, breed type, and sterilization status, odds of CCD were 6.47 times higher in dogs who were not active compared to those who were very active. When controlling for age, breed type, activity level, and other comorbidities, dogs with a history of neurological, eye, or ear disorders had higher odds of CCD. Lifespan quartile analysis showed excellent discriminating ability between CCD positive and negative dogs. Weight-based lifespan quartile estimation could therefore serve as a tool to inform CCD screening by veterinarians.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Stress-induced protein disaggregation in the endoplasmic reticulum catalysed by BiP

Protein synthesis is supported by cellular machineries that ensure polypeptides fold to their native conformation, whilst eliminating misfolded, aggregation prone species. Protein aggregation underlies pathologies including neurodegeneration. Aggregates' formation is antagonised by molecular chaperones, with cytoplasmic machinery resolving insoluble protein aggregates. However, it is unknown whether an analogous disaggregation system exists in the Endoplasmic Reticulum (ER) where ~30% of the proteome is synthesised. Here we show that the ER of a variety of mammalian cell types, including neurons, is endowed with the capability to resolve protein aggregates under stress. Utilising a purpose-developed protein aggregation probing system with a sub-organellar resolution, we observe steady-state aggregate accumulation in the ER. Pharmacological induction of ER stress does not augment aggregates, but rather stimulate their clearance within hours. We show that this dissagregation activity is catalysed by the stress-responsive ER molecular chaperone – BiP. This work reveals a hitherto unknow, non-redundant strand of the proteostasis-restorative ER stress response.

Heales
HEALTHY LIFE EXTENSION SOCIETY

A human brain vascular atlas reveals diverse mediators of Alzheimer's risk

The human brain vasculature is of great medical importance: its dysfunction causes disability and death[1], and the specialized structure it forms—the blood–brain barrier—impedes the treatment of nearly all brain disorders[2,3]. Yet so far, we have no molecular map of the human brain vasculature. Here we develop vessel isolation and nuclei extraction for sequencing (VINE-seq) to profile the major vascular and perivascular cell types of the human brain through 143,793 single-nucleus transcriptomes from 25 hippocampus and cortex samples of 9 individuals with Alzheimer's disease and 8 individuals with no cognitive impairment. We identify brain-region- and species-enriched genes and pathways. We reveal molecular principles of human arteriovenous organization, recapitulating a gradual endothelial and punctuated mural cell continuum. We discover two subtypes of human pericytes, marked by solute transport and extracellular matrix (ECM) organization; and define perivascular versus meningeal fibroblast specialization. In Alzheimer's disease, we observe selective vulnerability of ECM-maintaining pericytes and gene expression patterns that implicate dysregulated blood flow. With an expanded survey of brain cell types, we find that 30 of the top 45 genes that have been linked to Alzheimer's disease risk by genome-wide association studies (GWASs) are expressed in the human brain vasculature, and we confirm this by immunostaining. Vascular GWAS genes map to endothelial protein transport, adaptive immune and ECM pathways. Many are microglia-specific in mice, suggesting a partial evolutionary transfer of Alzheimer's disease risk. Our work uncovers the molecular basis of the human brain vasculature, which will inform our understanding of overall brain health, disease and therapy.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Brain charts for the human lifespan

R. A. I. Bethlehem, J. Seidlitz, ... A. F. Alexander-Bloch + Show authors

Over the past few decades, neuroimaging has become a ubiquitous tool in basic research and clinical studies of the human brain. However, no reference standards currently exist to quantify individual differences in neuroimaging metrics over time, in contrast to growth charts for anthropometric traits such as height and weight[1]. Here we assemble an interactive open resource to benchmark brain morphology derived from any current or future sample of MRI data (http://www.brainchart.io/). With the goal of basing these reference charts on the largest and most inclusive dataset available, acknowledging limitations due to known biases of MRI studies relative to the diversity of the global population, we aggregated 123,984 MRI scans, across more than 100 primary studies, from 101,457 human participants between 115 days post-conception to 100 years of age. MRI metrics were quantified by centile scores, relative to non-linear trajectories[2] of brain structural changes, and rates of change, over the lifespan. Brain charts identified previously unreported neurodevelopmental milestones[3], showed high stability of individuals across longitudinal assessments, and demonstrated robustness to technical and methodological differences between primary studies. Centile scores showed increased heritability compared with non-centiled MRI phenotypes, and provided a standardized measure of atypical brain structure that revealed patterns of neuroanatomical variation across neurological and psychiatric disorders. In summary, brain charts are an essential step towards robust quantification of individual variation benchmarked to normative trajectories in multiple, commonly used neuroimaging phenotypes.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Necroptosis inhibition counteracts axonal degeneration, cognitive decline and key hallmarks of aging, promoting brain rejuvenation

Macarena S. Arrázola, Matías Lira, Gabriel Quiroz, Somya Iqbal, Samantha L Eaton, Rachel A Kline, Douglas J Lamont, Hernán Huerta, Gonzalo Ureta, Sebastián Bernales, J César Cárdenas, Waldo Cerpa, Thomas M. Wishart, Felipe A. Court

Age is the main risk factor for the development of neurodegenerative diseases. In the aged brain, axonal degeneration is an early pathological event, preceding neuronal dysfunction, and cognitive disabilities. Necroptosis activation mediates degeneration of injured axons, but whether necroptosis triggers neurodegeneration and cognitive impairment along aging is unknown. Here we show necroptosis activation in hippocampal axons during aging. Loss of the necroptotic effector *Mlkl* was sufficient to delay age-associated axonal degeneration, protecting against decreased synaptic transmission and memory decline in aged mice. Moreover, short-term pharmacologic inhibition of necroptosis in aged mice reverted structural and functional hippocampal impairment. Finally, a quantitative proteomic analysis revealed that necroptosis inhibition leads to an overall improvement of the aged hippocampal proteome, including molecular biofunctions associated with brain rejuvenation. Our results demonstrate that necroptosis contributes to the functional decline of the aged brain, and necroptosis inhibition constitute a potential geroprotective strategy to treat age-related disabilities.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Fecal microbiota transfer between young and aged mice reverses hallmarks of the aging gut, eye, and brain

Background

Altered intestinal microbiota composition in later life is associated with inflammaging, declining tissue function, and increased susceptibility to age-associated chronic diseases, including neurodegenerative dementias. Here, we tested the hypothesis that manipulating the intestinal microbiota influences the development of major comorbidities associated with aging and, in particular, inflammation affecting the brain and retina.

Methods

Using fecal microbiota transplantation, we exchanged the intestinal microbiota of young (3 months), old (18 months), and aged (24 months) mice. Whole metagenomic shotgun sequencing and metabolomics were used to develop a custom analysis workflow, to analyze the changes in gut microbiota composition and metabolic potential. Effects of age and microbiota transfer on the gut barrier, retina, and brain were assessed using protein assays, immunohistology, and behavioral testing.

Results

We show that microbiota composition profiles and key species enriched in young or aged mice are successfully transferred by FMT between young and aged mice and that FMT modulates resulting metabolic pathway profiles. The transfer of aged donor microbiota into young mice accelerates age-associated central nervous system (CNS) inflammation, retinal inflammation, and cytokine signaling and promotes loss of key functional protein in the eye, effects which are coincident with increased intestinal barrier permeability. Conversely, these detrimental effects can be reversed by the transfer of young donor microbiota.

Conclusions

These findings demonstrate that the aging gut microbiota drives detrimental changes in the gut–brain and gut–retina axes suggesting that microbial modulation may be of therapeutic benefit in preventing inflammation-related tissue decline in later life.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Full geroprotection from brief rapamycin treatment by persistently increased intestinal autophagy

Paula Juricic, Yu-Xuan Lu, Thomas Leech, Lisa F. Drews, Jonathan Paulitz, Jiongming Lu, Tobias Nespital, Sina Azami, Jennifer C. Regan, Emilie Funk, Jenny Fröhlich, Sebastian Grönke, Linda Partridge

The licensed drug rapamycin has potential to be repurposed for geroprotection. A key challenge is to avoid adverse side-effects from continuous dosing regimes. Here we show a profound memory effect of brief, early rapamycin treatment of adults, which extended lifespan in *Drosophila* to the same degree as lifelong dosing. Lasting memory of earlier rapamycin treatment was mediated by elevated autophagy in enterocytes of the gut, accompanied by increased intestinal lysosomal alpha-mannosidase V (LManV) and lysozyme levels and improved structure and function of the ageing intestine. Brief elevation of autophagy itself induced a long-term increase in autophagy. In mice, a short-term, 3-month treatment in early adulthood also induced a memory effect, with enhanced autophagy in Paneth cells, improved Paneth cell architecture and gut barrier function at levels induced by chronic treatment, even 6 months after rapamycin was withdrawn. Past rapamycin treatment also enhanced the regenerative potential of aged intestine in intestinal organoids. Full geroprotective effects of chronic rapamycin treatment can thus be obtained with a brief pulse of the drug.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

A Physiology Clock for Human Aging

Sergiy Libert, Alex Chekholko, Cynthia Kenyon

Why people age at different rates is a fundamental unsolved problem in biology. We created a model that predicts an individual's age, taking as input physiological traits that change with age in the large UK Biobank dataset, such as blood pressure, blood metabolites, strength, and stimulus-reaction time. The model's Root Mean Square Error of age prediction (RMSE) is less than 5 years. We argue that the difference between calculated "biological" age and actual age (ΔAge) reflects an individual's relative youthfulness and possibly their rate of aging. Validating this interpretation, people predicted to be physiologically young for their age have a lower subsequent mortality rate and a higher parental age at death, even though no mortality data were used to calculate ΔAge. A Genome-Wide Association Study (GWAS) of ΔAge, and analysis of environmental factors associated with ΔAge identified known as well as new factors that may influence human aging, including genes involved in synapse biology and a tendency to play computer games. We identify 12 readily-measured physiological traits that together assess a person's biological age and may be used clinically to evaluate therapeutics designed to slow aging and extend healthy life.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Genetic loci and metabolic states associated with murine epigenetic aging

Changes in DNA methylation (DNAm) are linked to aging. Here, we profile highly conserved CpGs in 339 predominantly female mice belonging to the BXD family for which we have deep longevity and genomic data. We use a 'pan-mammalian' microarray that provides a common platform for assaying the methylome across mammalian clades. We computed epigenetic clocks and tested associations with DNAm entropy, diet, weight, metabolic traits, and genetic variation. We describe the multifactorial variance of methylation at these CpGs and show that high-fat diet augments the age-related changes. Entropy increases with age. The progression to disorder, particularly at CpGs that gain methylation over time, was predictive of genotype-dependent life expectancy. The longer-lived BXD strains had comparatively lower entropy at a given age. We identified two genetic loci that modulate epigenetic age acceleration (EAA): one on chromosome (Chr) 11 that encompasses the *Erbb2/Her2* oncogenic region, and the other on Chr19 that contains a cytochrome P450 cluster. Both loci harbor genes associated with EAA in humans, including *STXBP4*, *NKX2*-3, and *CUTC*. Transcriptome and proteome analyses revealed correlations with oxidation-reduction, metabolic, and immune response pathways. Our results highlight concordant loci for EAA in humans and mice, and demonstrate a tight coupling between the metabolic state and epigenetic aging.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Epigenetic clock and methylation studies in marsupials: opossums, Tasmanian devils, kangaroos, and wallabies

Steve Horvath, Amin Haghani, Joseph A. Zoller, Ken Raj, Ishani Sinha, Todd R. Robeck, Pete Black, Aidan Couzens, Clive Lau, Meghety Manoyan, Yadiamaris Aviles Ruiz, Annais Talbott, Katherine Belov, Carolyn J. Hogg & Karen E. Sears

The opossum (*Monodelphis domestica*), with its sequenced genome, ease of laboratory care and experimental manipulation, and unique biology, is the most used laboratory marsupial. Using the mammalian methylation array, we generated DNA methylation data from $n = 100$ opossum samples from the ear, liver, and tail. We contrasted postnatal development and later aging effects in the opossum methylome with those in mouse (*Mus musculus*, C57BL/6 J strain) and other marsupial species such as Tasmanian devil, kangaroos, and wallabies. While the opossum methylome is similar to that of mouse during postnatal development, it is distinct from that shared by other mammals when it comes to the age-related gain of methylation at target sites of polycomb repressive complex 2. Our immunohistochemical staining results provide additional support for the hypothesis that PRC2 activity increases with later aging in mouse tissues but remains constant in opossum tissues. We present several epigenetic clocks for opossums that are distinguished by their compatibility with tissue type (pan-tissue and blood clock) and species (opossum and human). Two dual-species human-opossum pan-tissue clocks accurately measure chronological age and relative age, respectively. The human-opossum epigenetic clocks are expected to provide a significant boost to the attractiveness of opossum as a biological model. Additional epigenetic clocks for Tasmanian devil, red kangaroos and other species of the genus *Macropus* may aid species conservation efforts.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

3D Reconstructions of Mouse Skeletal Muscle Reveal a Decrease in the MICOS Complex and Altered Mitochondrial Networks

Background Skeletal muscle gradually loses mass, strength, endurance, and oxidative capacity during aging. Studies of bioenergetics and protein turnover show that mitochondria mediate this decline in function. Mitochondria cristae are essential for the production of ATP. While mitochondrial aging is associated with endoplasmic reticulum stress, fragmented mitochondria, and decreased mitochondrial capacity, the genes associated with morphological changes in mitochondria during aging still requires further elucidation Further, it is not completely understood how 3D mitochondrial networks and the specialization of mitochondria are altered during aging.

Methods We measured changes in mitochondrial morphology and mitochondrial connectivity during the aging of the mouse gastrocnemius muscle through serial block facing-scanning electron microscopy and 3D reconstruction. Nanotunnels were also measured through 3D reconstruction. CRISPR/Cas9 KO was performed to examine changes in mitochondria upon loss of the mitochondrial contact site and cristae organizing system (MICOS) complex and optic atrophy 1 (OPA-1). Metabolomics were used to find key metabolite pathways changed upon off of the MICOS complex.

Results We found changes in mitochondrial network configuration, nanotunneling, size, shape, number, contact sites, cristae organizing system (MICOS) dynamics and gene expression in skeletal muscle during aging. We also found an association of OPA-1 and the MICOS complex in the gastrocnemius with mitochondrial aging. Further, the loss of the MICOS complex was linked with decreased oxidative capacity, and altered mitochondrial metabolism.

Conclusions To our knowledge, studies of mitochondrial changes in skeletal muscle throughout aging remains limited. 3D reconstructions of nanotunnels elucidated novel patterns of mitochondrial aging in skeletal muscle. MICOS proteins decreased with age and mitochondrial morphology was similar between aged skeletal muscle and that of young mice with MICOS protein loss. In tandem, our data suggest a relationship between the MICOS complex and aging, which could be potentially linked to disease sates with additional 3D reconstruction.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Altered levels of circulating mitochondrial DNA in elderly people with sarcopenia: Association with mitochondrial impairment

Background: Age-related chronic inflammatory process is often referred to as "inflammaging", which had been described in several human disorders, including sarcopenia. Recently, mitochondrial DNA (MtDNA) has moved into the spotlight as a "damage-associated molecular pattern" (DAMP) agent that can potentially elicit inflammation. Yet, the roles of this mitochondrial DAMP have never been investigated in sarcopenia.

Design: Cross-sectional study.

Participants: From January 2021 to June 2021, elderly outpatients ≥65 years and able to finish a comprehensive geriatric assessment were recruited in our study.

Methods: Participants were divided into sarcopenia group and non-sarcopenia group according to the DXA scans and grip strength. Genomic DNA was extracted from plasma and peripheral blood mononuclear cells (PBMCs), and changes in MtDNA copies were quantified using qPCR. Plasma levels of inflammatory cytokines were measured using ELISA kits. Loss of mitochondrial membrane potential ($\Delta\psi m$) in PBMCs was analyzed using the fluorescent probe JC-1.

Results: Participants with sarcopenia were significantly older, more likely to be physically inactive, and had higher levels of circulating cell-free MtDNA (ccf-MtDNA) (all $p < 0.05$). After adjusting for potential confounders, ccf-MtDNA was independently associated with increased odds of sarcopenia (adjusted odds ratio (AOR), 1.576; $p = 0.009$). Furthermore, ROC curve analysis showed that ccf-MtDNA had an area under the curve (AUC) of 0.726 (95% CI: 0.607-0.844; $p < 0.05$) for distinguishing elderly subjects from sarcopenia. Compared with non-sarcopenia subjects, plasma interleukin (IL)-6 and IL-8 were significantly higher in sarcopenia subjects (both $p < 0.05$). By performing a correlation test, it was found that the level of IL-6 was positively correlated with ccf-MtDNA ($r = 0.301$; $p < 0.05$). Then, PBMCs were used as surrogates for mitochondria-rich cells, and the results showed that the relative amplification of MtDNA in PBMCs was significantly reduced ($p < 0.05$), whereas the depolarization of $\Delta\psi m$ was significantly increased in sarcopenia subjects ($p < 0.05$).

Conclusions: Taken together, our data suggested that circulating MtDNA might be a novel and important source of inflammatory stimuli potentially relevant for sarcopenia in elderly people, and this would provide an attractive therapeutic target to improve this disease.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Heteroplasmic mitochondrial DNA variants in cardiovascular diseases

Claudia Calabrese, Angela Pyle, Helen Griffin, Jonathan Coxhead, Rafiqul Hussain, Peter S Braund, Linxin Li, Annette Burgess, Patricia B Munroe, Louis Little, Helen R Warren, Claudia Cabrera, Alistair Hall, [...], Patrick F. Chinnery [view all]

Version 2 Published: April 1, 2022 • https://doi.org/10.1371/journal.pgen.1010068

Article | Authors | Metrics | Comments | Media Coverage

Abstract

Mitochondria are implicated in the pathogenesis of cardiovascular diseases (CVDs) but the reasons for this are not well understood. Maternally-inherited population variants of mitochondrial DNA (mtDNA) which affect all mtDNA molecules (homoplasmic) are associated with cardiometabolic traits and the risk of developing cardiovascular disease. However, it is not known whether mtDNA mutations only affecting a proportion of mtDNA molecules (heteroplasmic) also play a role. To address this question, we performed a high-depth (~1000-fold) mtDNA sequencing of blood DNA in 1,399 individuals with hypertension (HTN), 1,946 with ischemic heart disease (IHD), 2,146 with ischemic stroke (IS), and 723 healthy controls. We show that the *per* individual burden of heteroplasmic single nucleotide variants (mtSNVs) increases with age. The age-effect was stronger for low-level heteroplasmies (heteroplasmic fraction, HF, 5–10%), likely reflecting acquired somatic events based on trinucleotide mutational signatures. After correcting for age and other confounders, intermediate heteroplasmies (HF 10–95%) were more common in hypertension, particularly involving non-synonymous variants altering the amino acid sequence of essential respiratory chain proteins. These findings raise the possibility that heteroplasmic mtSNVs play a role in the pathophysiology of hypertension.

System-level metabolic modeling facilitates unveiling metabolic signature in exceptional longevity

Gong-Hua Li, Feifei Han, Fu-Hui Xiao, Kang-Su-Yun Gu, Qiu Shen, Weihong Xu, Wen-Xing Li, Yan-Li Wang, Bin Liang, Jing-Fei Huang, Wenzhong Xiao, Qing-Peng Kong

First published: 27 March 2022 | https://doi.org/10.1111/acel.13595

Abstract

Although it is well known that metabolic control plays a crucial role in regulating the health span and life span of various organisms, little is known for the systems metabolic profile of centenarians, the paradigm of human healthy aging and longevity. Meanwhile, how to well characterize the system-level metabolic states in an organism of interest remains to be a major challenge in systems metabolism research. To address this challenge and better understand the metabolic mechanisms of healthy aging, we developed a method of genome-wide precision metabolic modeling (GPMM) which is able to quantitatively integrate transcriptome, proteome and kinetome data in predictive modeling of metabolic networks. Benchmarking analysis showed that GPMM successfully characterized metabolic reprogramming in the NCI-60 cancer cell lines; it dramatically improved the performance of the modeling with an R^2 of 0.86 between the predicted and experimental measurements over the performance of existing methods. Using this approach, we examined the metabolic networks of a Chinese centenarian cohort and identified the elevated fatty acid oxidation (FAO) as the most significant metabolic feature in these long-lived individuals. Evidence from serum metabolomics supports this observation. Given that FAO declines with normal aging and is impaired in many age-related diseases, our study suggests that the elevated FAO has potential to be a novel signature of healthy aging of humans.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Proteomes of primary skin fibroblasts from healthy individuals reveal altered cell responses across the life span

Changes in the proteome of different human tissues with advancing age are poorly characterized. Here, we studied the proteins present in primary skin fibroblasts collected from 82 healthy individuals across a wide age spectrum (22–89 years old) who participated in the GESTALT (Genetic and Epigenetic Signatures of Translational Aging Laboratory Testing) study of the National Institute on Aging, NIH. Proteins were extracted from lysed fibroblasts and subjected to liquid chromatography-mass spectrometry analysis, and the expression levels of 9341 proteins were analyzed using linear regression models. We identified key pathways associated with skin fibroblast aging, including autophagy, scavenging of reactive oxygen species (ROS), ribosome biogenesis, DNA replication, and DNA repair. Changes in these prominent pathways were corroborated using molecular and cell culture approaches. Our study establishes a framework of the global proteome governing skin fibroblast aging and points to possible biomarkers and therapeutic targets.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Projecting prevalence of frailty and dementia and the economic cost of care in Japan from 2016 to 2043: a microsimulation modelling study

Background

Dementia and frailty often accompany one another in older age, requiring complex care and resources. Available projections provide little information on their joint impact on future health-care need from different segments of society and the associated costs. Using a newly developed microsimulation model, we forecast this situation in Japan as its population ages and decreases in size.

Methods

In this microsimulation modelling study, we built a model that simulates an individual's status transition across 11 chronic diseases (including diabetes, coronary heart disease, and stroke) as well as depression, functional status, and self-reported health, by age, sex, and educational strata (less than high school, high school, and college and higher), on the basis of nationally representative health surveys and existing cohort studies. Using the simulation results, we projected the prevalence of dementia and frailty, life expectancy with these conditions, and the economic cost for formal and informal care over the period 2016–43 in the population of Japan aged 60 years and older.

Findings

Between 2016 and 2043, life expectancy at age 65 years will increase from 23·7 years to 24·9 years in women and from 18·7 years to 19·9 years in men. Years spent with dementia will decrease from 4·7 to 3·9 years in women and 2·2 to 1·4 years in men. By contrast, years spent with frailty will increase from 3·7 to 4·0 years for women and 1·9 to 2·1 for men, and across all educational groups. By 2043, approximately 29% of women aged 75 years and older with a less than high school education are estimated to have both dementia and frailty, and so will require complex care. The expected need for health care and formal long-term care is anticipated to reach costs of US$125 billion for dementia and $97 billion for frailty per annum in 2043 for the country.

Interpretation

Japan's Government and policy makers should consider the potential social challenges in caring for a sizable population of older people with frailty and dementia, and a widening disparity in the burden of those conditions by sex and by educational status. The future burden of dementia and frailty should be countered not only by curative and preventive technology innovation, but also by social policies to mitigate the health gap.

C. elegans aging research

Heales
HEALTHY LIFE EXTENSION SOCIETY

Metabolomics reveals the impact of the saturation of dietary lipids on the aging and longevity of *C. elegans*

Yanan Wang [1], Jiachen Shi [1], Fan Jiang [1], Yong-Jiang Xu [1], Yuanfa Liu [1]

Affiliations + expand

PMID: 35411365 DOI: 10.1039/d2mo00041e

Abstract

Dietary lipids play an important role in human health, but their influence on aging and longevity remains to be ascertained. This study tests the hypothesis that the consumption of fats with elevated unsaturation might slow down aging and prolong lifespan better than that with greater saturation. The metabolomic analysis of *Caenorhabditis elegans* (*C. elegans*) administrated with different dietary oils (palm oil, rapeseed oil, sunflower oil and linseed oil) revealed novel changes in lipid, carbohydrate, amino acid and purine metabolism. Elevated levels of eicosanoic acid, stearic acid, palmitic acid, L-isoleucine, L-lysine, L-tyrosine, and D-fructose, along with decreased content of arachidonic acid (ARA), eicosapentaenoic acid (EPA), and alpha-linolenic acid (ALA) were found in *C. elegans* with the intake of dietary oils with higher saturation. Declined gene expression levels of *daf-2* and *akt-1*, as well as increased levels of *daf-16*, *sod-3*, *hsp-16.2*, *hsf-1*, *nhr-80*, *fat-5*, *fat-6*, and *fat-7*, were noted in the higher unsaturation dietary oil groups. Carbohydrates and amino acids showed moderate to strong correlations with *daf-2* and *akt-1* (negative), as well as *daf-16*, *sod-3*, *hsp-16.2*, and *hsf-1* (positive). Otherwise, our data suggested significant positive relationships between polyunsaturated fatty acids (ARA, EPA, ALA) and *nhr-80*, *fat-5*, *fat-6* and *fat-7*. Taken together, this study demonstrates that unsaturated dietary oils can slow down aging and prolong the lifespan of *C. elegans via* the insulin signaling pathway and the biosynthesis of unsaturated fatty acids.

REVIEWS/COMMENTS/ METHODS/EDITORIALS

Heales
HEALTHY LIFE EXTENSION SOCIETY

Dysregulated RNA processing and metabolism: a new hallmark of ageing and provocation for cellular senescence

The human genome is capable of producing hundreds of thousands of different proteins and non-coding RNAs from <20 000 genes, in a co-ordinated and regulated fashion. This is achieved by a collection of phenomena known as mRNA processing and metabolism, and encompasses events in the life cycle of an RNA from synthesis to degradation. These factors are critical determinants of cellular adaptability and plasticity, which allows the cell to adjust its transcriptomic output in response to its internal and external environment. Evidence is building that dysfunctional RNA processing and metabolism may be a key contributor to the development of cellular senescence. Senescent cells by definition have exited cell cycle, but have gained functional features such as the secretion of the senescence-associated secretory phenotype (SASP), a known driver of chronic disease and perhaps even ageing itself. In this review, I will outline the impact of dysregulated mRNA processing and metabolism on senescence and ageing at the level of genes, cells and systems, and describe the mechanisms by which progressive deterioration in these processes may impact senescence and organismal ageing. Finally, I will present the evidence implicating this important process as a new hallmark of ageing, which could be harnessed in the future to develop new senotherapeutic interventions for chronic disease.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Making sense of the ageing methylome

Kirsten Seale, Steve Horvath, Andrew Teschendorff, Nir Eynon & Sarah Voisin

Nature Reviews Genetics (2022) | Cite this article

1167 Accesses | **49** Altmetric | Metrics

Abstract

Over time, the human DNA methylation landscape accrues substantial damage, which has been associated with a broad range of age-related diseases, including cardiovascular disease and cancer. Various age-related DNA methylation changes have been described, including at the level of individual CpGs, such as differential and variable methylation, and at the level of the whole methylome, including entropy and correlation networks. Here, we review these changes in the ageing methylome as well as the statistical tools that can be used to quantify them. We detail the evidence linking DNA methylation to ageing phenotypes and the longevity strategies aimed at altering both DNA methylation patterns and machinery to extend healthspan and lifespan. Lastly, we discuss theories on the mechanistic causes of epigenetic ageing.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Geroscience-guided repurposing of FDA-approved drugs to target aging: A proposed process and prioritization

Ameya S. Kulkarni, Sandra Aleksic, David M. Berger, Felipe Sierra, George A. Kuchel, Nir Barzilai

Common chronic diseases represent the greatest driver of rising healthcare costs, as well as declining function, independence, and quality of life. Geroscience-guided approaches seek to delay the onset and progression of multiple chronic conditions by targeting fundamental biological pathways of aging. This approach is more likely to improve overall health and function in old age than treating individual diseases, by addressing aging the largest and mostly ignored risk factor for the leading causes of morbidity in older adults. Nevertheless, challenges in repurposing existing and moving newly discovered interventions from the bench to clinical care have impeded the progress of this potentially transformational paradigm shift. In this article, we propose the creation of a standardized process for evaluating FDA-approved medications for their geroscience potential. Criteria for systematically evaluating the existing literature that spans from animal models to human studies will permit the prioritization of efforts and financial investments for translating geroscience and allow immediate progress on the design of the next Targeting Aging with MEtformin (TAME)-like study involving such candidate gerotherapeutics.

Pharmaceutical and nutraceutical activation of FOXO3 for healthy longevity

Rebecca L McIntyre [1], Yasmine J Liu [1], Man Hu [1], Brian J Morris [2], Bradley J Willcox [3], Timothy A Donlon [4], Riekelt H Houtkooper [1], Georges E Janssens [5]

Affiliations + expand

PMID: 35421606 DOI: 10.1016/j.arr.2022.101621

Free article

Abstract

Life expectancy has increased substantially over the last 150 years. Yet this means that now most people also spend a greater length of time suffering from various age-associated diseases. As such, delaying age-related functional decline and extending healthspan, the period of active older years free from disease and disability, is an overarching objective of current aging research. Geroprotectors, compounds that target pathways that causally influence aging, are increasingly recognized as a means to extend healthspan in the aging population. Meanwhile, FOXO3 has emerged as a geroprotective gene intricately involved in aging and healthspan. FOXO3 genetic variants are linked to human longevity, reduced disease risks, and even self-reported health. Therefore, identification of FOXO3-activating compounds represents one of the most direct candidate approaches to extending healthspan in aging humans. In this work, we review compounds that activate FOXO3, or influence healthspan or lifespan in a FOXO3-dependent manner. These compounds can be classified as pharmaceuticals, including PI3K/AKT inhibitors and AMPK activators, antidepressants and antipsychotics, muscle relaxants, and HDAC inhibitors, or as nutraceuticals, including primary metabolites involved in cell growth and sustenance, and secondary metabolites including extracts, polyphenols, terpenoids, and other purified natural compounds. The compounds documented here provide a basis and resource for further research and development, with the ultimate goal of promoting healthy longevity in humans.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Cardiovascular disease and the biology of aging

Shria Moturi, Shohini K. Ghosh-Choudhary, Toren Finkel

Show more

+ Add to Mendeley Share Cite

https://doi.org/10.1016/j.yjmcc.2022.04.005

Abstract

The incidence and prevalence of a wide range of cardiovascular diseases increases as a function of age. This well-established epidemiological relationship suggests that chronological aging might contribute or increase susceptibility to varied conditions such as atherosclerosis, vascular stiffening or heart failure. Here, we explore the mechanistic links that connect both rare and common cardiovascular conditions to the basic biology of aging. These links provide a rational basis to begin to develop a new set of therapeutics targeting the fundamental mechanisms underlying the aging process and suggest that in the near future, age itself might become a modifiable cardiovascular risk factor.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Heterochronic parabiosis: a valuable tool to investigate cellular senescence and other hallmarks of aging

Matthew J Yousefzadeh [1 2], Paul D Robbins [1 2], Derek M Huffman [3 4]

Affiliations + expand

PMID: 35417855 PMCID: PMC9037264 DOI: 10.18632/aging.204015

Free PMC article

Abstract

Parabiosis is a well-established method to facilitate a shared blood supply between two conjoined animals. In particular, the pairing of mice of dissimilar ages, termed heterochronic parabiosis, has been used extensively for differentiating cell autonomous and non-autonomous mechanisms of aging. Analysis of heterochronic parabionts also has helped to identify individual circulating factors that may act as either pro- or anti-geronics. Heterochronic parabiosis also has proven to be a valuable experimental system to evaluate the effects of specific hallmarks of aging on the process of aging. For example, heterochronic parabiosis was used recently to examine whether cellular senescence was driven via cell autonomous and/or non-autonomous mechanisms. As anticipated, markers of cellular senescence were elevated in old isochronically-paired mice relative to young controls. However, compared to old isochronically paired mice, the senescent cell burden was reduced in multiple tissues of old parabionts joined with young mice. This suggests that the rejuvenation of cells and tissues in old mice by exposure to young blood could be mediated, in part, through suppression or immune clearance of senescent cells. Conversely, young heterochronic parabionts showed increased markers of cellular senescence, demonstrating that exposure to an old circulation is able to drive senescence through a cell non-autonomous mechanism(s), likely contributing to accelerated aging in the young mice. Thus, heterochronic parabiosis is still an important methodology that should continue to be leveraged for evaluating other hallmarks of aging and their mechanisms.

OTHER RESEARCH & REVIEWS

Heales
HEALTHY LIFE EXTENSION SOCIETY

Testing the reproducibility and robustness of the cancer biology literature by robot

Katherine Roper, A. Abdel-Rehim, Sonya Hubbard, Martin Carpenter, Andrey Rzhetsky, Larisa Soldatova and Ross D. King ✉

Published: 06 April 2022 | https://doi.org/10.1098/rsif.2021.0821

Abstract

Scientific results should not just be 'repeatable' (replicable in the same laboratory under identical conditions), but also 'reproducible' (replicable in other laboratories under similar conditions). Results should also, if possible, be 'robust' (replicable under a wide range of conditions). The reproducibility and robustness of only a small fraction of published biomedical results has been tested; furthermore, when reproducibility is tested, it is often not found. This situation is termed 'the reproducibility crisis', and it is one the most important issues facing biomedicine. This crisis would be solved if it were possible to automate reproducibility testing. Here, we describe the semi-automated testing for reproducibility and robustness of simple statements (propositions) about cancer cell biology automatically extracted from the literature. From 12 260 papers, we automatically extracted statements predicted to describe experimental results regarding a change of gene expression in response to drug treatment in breast cancer, from these we selected 74 statements of high biomedical interest. To test the reproducibility of these statements, two different teams used the laboratory automation system Eve and two breast cancer cell lines (MCF7 and MDA-MB-231). Statistically significant evidence for repeatability was found for 43 statements, and significant evidence for reproducibility/robustness in 22 statements. In two cases, the automation made serendipitous discoveries. The reproduced/robust knowledge provides significant insight into cancer. We conclude that semi-automated reproducibility testing is currently achievable, that it could be scaled up to generate a substantive source of reliable knowledge and that automation has the potential to mitigate the reproducibility crisis.

Heales
HEALTHY LIFE EXTENSION SOCIETY

An open quantum systems approach to proton tunnelling in DNA

Louie Slocombe, Marco Sacchi & Jim Al-Khalili

Communications Physics **5**, Article number: 109 (2022) | Cite this article

Abstract

One of the most important topics in molecular biology is the genetic stability of DNA. One threat to this stability is proton transfer along the hydrogen bonds of DNA that could lead to tautomerisation, hence creating point mutations. We present a theoretical analysis of the hydrogen bonds between the Guanine-Cytosine (G-C) nucleotide, which includes an accurate model of the structure of the base pairs, the quantum dynamics of the hydrogen bond proton, and the influence of the decoherent and dissipative cellular environment. We determine that the quantum tunnelling contribution to the proton transfer rate is several orders of magnitude larger than the classical over-the-barrier hopping. Due to the significance of the quantum tunnelling even at biological temperatures, we find that the canonical and tautomeric forms of G-C inter-convert over timescales far shorter than biological ones and hence thermal equilibrium is rapidly reached. Furthermore, we find a large tautomeric occupation probability of 1.73×10^{-4}, suggesting that such proton transfer may well play a far more important role in DNA mutation than has hitherto been suggested. Our results could have far-reaching consequences for current models of genetic mutations.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Skin cells undergo asynthetic fission to expand body surfaces in zebrafish

Keat Ying Chan, Ching-Cher Sanders Yan, Hsiao-Yuh Roan, Shao-Chun Hsu, Tzu-Lun Tseng, Chung-Der Hsiao, Chao-Ping Hsu & Chen-Hui Chen

Nature **605**, 119–125 (2022) | Cite this article

23k Accesses | **1** Citations | **605** Altmetric | Metrics

Abstract

As an animal's surface area expands during development, skin cell populations must quickly respond to maintain sufficient epithelial coverage. Despite much progress in understanding of skin cell behaviours in vivo[1,2], it remains unclear how cells collectively act to satisfy coverage demands at an organismic level. Here we created a multicolour cell membrane tagging system, *palmskin*, to monitor the entire population of superficial epithelial cells (SECs) in developing zebrafish larvae. Using time-lapse imaging, we found that many SECs readily divide on the animal body surface; during a specific developmental window, a single SEC can produce a maximum of four progeny cells over its lifetime on the surface of the animal. Remarkably, EdU assays, DNA staining and hydroxyurea treatment showed that these terminally differentiated skin cells continue splitting despite an absence of DNA replication, causing up to 50% of SECs to exhibit reduced genome size. On the basis of a simple mathematical model and quantitative analyses of cell volumes and apical surface areas, we propose that 'asynthetic fission' is used as an efficient mechanism for expanding epithelial coverage during rapid growth. Furthermore, global or local manipulation of body surface growth affects the extent and mode of SEC division, presumably through tension-mediated activation of stretch-activated ion channels. We speculate that this frugal yet flexible mode of cell proliferation might also occur in contexts other than zebrafish skin expansion.