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Scientific News
7th of June 2020
Sven Bulterijs

Business/Conferences/ General news

A hydroxychloroquine study is being audited. AP PHOTO/JOHN LOCHER

A mysterious company's coronavirus papers in top medical journals may be unraveling

By Kelly Servick, Martin Enserink | Jun. 2, 2020 , 7:55 PM

***Science*'s COVID-19 reporting is supported by the Pulitzer Center.**

On its face, it was a major finding: Antimalarial drugs touted by the White House as possible COVID-19 treatments looked to be not just ineffective, but downright deadly. **A study published on 22 May in *The Lancet*** used hospital records procured by a little-known data analytics company called Surgisphere to conclude that coronavirus patients taking chloroquine or hydroxychloroquine were more likely to show an irregular heart rhythm—**a known side effect thought to be rare**—and were more likely to die in the hospital.

A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19

BACKGROUND

Coronavirus disease 2019 (Covid-19) occurs after exposure to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). For persons who are exposed, the standard of care is observation and quarantine. Whether hydroxychloroquine can prevent symptomatic infection after SARS-CoV-2 exposure is unknown.

METHODS

We conducted a randomized, double-blind, placebo-controlled trial across the United States and parts of Canada testing hydroxychloroquine as postexposure prophylaxis. We enrolled adults who had household or occupational exposure to someone with confirmed Covid-19 at a distance of less than 6 ft for more than 10 minutes while wearing neither a face mask nor an eye shield (high-risk exposure) or while wearing a face mask but no eye shield (moderate-risk exposure). Within 4 days after exposure, we randomly assigned participants to receive either placebo or hydroxychloroquine (800 mg once, followed by 600 mg in 6 to 8 hours, then 600 mg daily for 4 additional days). The primary outcome was the incidence of either laboratory-confirmed Covid-19 or illness compatible with Covid-19 within 14 days.

RESULTS

We enrolled 821 asymptomatic participants. Overall, 87.6% of the participants (719 of 821) reported a high-risk exposure to a confirmed Covid-19 contact. The incidence of new illness compatible with Covid-19 did not differ significantly between participants receiving hydroxychloroquine (49 of 414 [11.8%]) and those receiving placebo (58 of 407 [14.3%]); the absolute difference was −2.4 percentage points (95% confidence interval, −7.0 to 2.2; P=0.35). Side effects were more common with hydroxychloroquine than with placebo (40.1% vs. 16.8%), but no serious adverse reactions were reported.

CONCLUSIONS

After high-risk or moderate-risk exposure to Covid-19, hydroxychloroquine did not prevent illness compatible with Covid-19 or confirmed infection when used as postexposure prophylaxis within 4 days after exposure. (Funded by David Baszucki and Jan Ellison Baszucki and others; ClinicalTrials.gov number, NCT04308668.)

OA Metformin Treatment Was Associated with Decreased Mortality in COVID-19 Patients with Diabetes in a Retrospective Analysis

Metformin was proposed to be a candidate for host-directed therapy for COVID-19. However, its efficacy remains to be validated. In this study, we compared the outcome of metformin users and nonusers in hospitalized COVID-19 patients with diabetes. Hospitalized diabetic patients with confirmed COVID-19 in the Tongji Hospital of Wuhan, China, from January 27, 2020 to March 24, 2020, were grouped into metformin and no-metformin groups according to the diabetic medications used. The demographics, characteristics, laboratory parameters, treatments, and clinical outcome in these patients were retrospectively assessed. A total of 283 patients (104 in the metformin and 179 in the no-metformin group) were included in this study. There were no significant differences between the two groups in gender, age, underlying diseases, clinical severity, and oxygen-support category at admission. The fasting blood glucose level of the metformin group was higher than that of the no-metformin group at admission and was under effective control in both groups after admission. Other laboratory parameters at admission and treatments after admission were not different between the two groups. The length of hospital stay did not differ between the two groups (21.0 days for metformin versus 19.5 days for no metformin, $P = 0.74$). However, in-hospital mortality was significantly lower in the metformin group (3/104 (2.9%) versus 22/179 (12.3%), $P = 0.01$). Antidiabetic treatment with metformin was associated with decreased mortality compared with diabetics not receiving metformin. This retrospective analysis suggests that metformin may offer benefits in patients with COVID-19 and that further study is indicated.

Remdesivir for the Treatment of Covid-19 — Preliminary Report

BACKGROUND

Although several therapeutic agents have been evaluated for the treatment of coronavirus disease 2019 (Covid-19), none have yet been shown to be efficacious.

METHODS

We conducted a double-blind, randomized, placebo-controlled trial of intravenous remdesivir in adults hospitalized with Covid-19 with evidence of lower respiratory tract involvement. Patients were randomly assigned to receive either remdesivir (200 mg loading dose on day 1, followed by 100 mg daily for up to 9 additional days) or placebo for up to 10 days. The primary outcome was the time to recovery, defined by either discharge from the hospital or hospitalization for infection-control purposes only.

RESULTS

A total of 1063 patients underwent randomization. The data and safety monitoring board recommended early unblinding of the results on the basis of findings from an analysis that showed shortened time to recovery in the remdesivir group. Preliminary results from the 1059 patients (538 assigned to remdesivir and 521 to placebo) with data available after randomization indicated that those who received remdesivir had a median recovery time of 11 days (95% confidence interval [CI], 9 to 12), as compared with 15 days (95% CI, 13 to 19) in those who received placebo (rate ratio for recovery, 1.32; 95% CI, 1.12 to 1.55; P<0.001). The Kaplan-Meier estimates of mortality by 14 days were 7.1% with remdesivir and 11.9% with placebo (hazard ratio for death, 0.70; 95% CI, 0.47 to 1.04). Serious adverse events were reported for 114 of the 541 patients in the remdesivir group who underwent randomization (21.1%) and 141 of the 522 patients in the placebo group who underwent randomization (27.0%).

CONCLUSIONS

Remdesivir was superior to placebo in shortening the time to recovery in adults hospitalized with Covid-19 and evidence of lower respiratory tract infection. (Funded by the National Institute of Allergy and Infectious Diseases and others; ACTT-1 ClinicalTrials.gov number, NCT04280705.)

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A cohort study to evaluate the effect of combination Vitamin D, Magnesium and Vitamin B12 (DMB) on progression to severe outcome in older COVID-19 patients.

Objective: To determine the clinical outcomes of older COVID-19 patients who received DMB compared to those who did not. We hypothesized that fewer patients administered DMB would require oxygen therapy and/or intensive care support than those who did not. Methodology: Cohort observational study of all consecutive hospitalized COVID-19 patients aged 50 and above in a tertiary academic hospital who received DMB compared to a recent cohort who did not. Patients were administered oral vitamin D3 1000 IU OD, magnesium 150mg OD and vitamin B12 500mcg OD (DMB) upon admission if they did not require oxygen therapy. Primary outcome was deterioration post-DMB administration leading to any form of oxygen therapy and/or intensive care support. Results: Between 15 January and 15 April 2020, 43 consecutive COVID-19 patients aged ≥50 were identified. 17 patients received DMB and 26 patients did not. Baseline demographic characteristics between the two groups were similar. Significantly fewer DMB patients than controls required initiation of oxygen therapy subsequently throughout their hospitalization (17.6% vs 61.5%, P=0.006). DMB exposure was associated with odds ratios of 0.13 (95% CI: 0.03 – 0.59) and 0.15 (95% CI: 0.03 – 0.93) for oxygen therapy need and/or intensive care support on univariate and multivariate analyses respectively. Conclusions: DMB combination in older COVID-19 patients was associated with a significant reduction in proportion of patients with clinical deterioration requiring oxygen support and/or intensive care support. This study supports further larger randomized control trials to ascertain the full benefit of DMB in ameliorating COVID-19 severity.

Letter: Thrombotic Neurovascular Disease in COVID-19 Patients FREE

Although the respiratory system is the primary target of the coronavirus, studies have demonstrated a strong tropism to the central nervous system (CNS).[1,2] The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infects cells by binding to the angiotensin-converting enzyme 2 (ACE2) receptor. This receptor is also found in the CNS and plays a crucial role in autoregulating cerebral perfusion pressure.[3,4] Additionally, epidemiological data demonstrated increased mortality due to cardiovascular and cerebrovascular diseases during flu pandemics due to a hypercoagulable state.[5,6] The triad of neuroinvasion of SARS-CoV-2, induction of hypercoagulable state,[5-9] and the inhibition of ACE2 blocking the formation of Angiotensin (1-7) serve as the pathophysiology for neurovascular insults.[3,4] We present a case series of coronavirus disease 2019 (COVID-19) patients from 2 health systems developing cerebrovascular insult.

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The role of high cholesterol in age-related COVID19 lethality

Coronavirus disease 2019 (COVID19) is a respiratory infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) originating in Wuhan China in 2019. The disease is notably severe in elderly and those with underlying chronic conditions. A molecular mechanism that explains why the elderly are vulnerable and why children are resistant is largely unknown. Understanding these differences is critical for safeguarding the vulnerable and guiding effective policy and treatments. Here we show loading cells with cholesterol from blood serum using the cholesterol transport protein apolipoprotein E (apoE) enhances the endocytic entry of pseudotyped SARS-CoV-2. Super resolution imaging of the SARS-CoV-2 entry point with high cholesterol showed almost twice the total number of viral entry points. The cholesterol concomitantly traffics angiotensinogen converting enzyme (ACE2) to the viral entry site where SARS-CoV-2 docks to properly exploit entry into the cell. Cholesterol also increased binding of SARS-CoV-2 receptor binding domains. In mouse lung we found age and high fat diet induced cholesterol loading into lung tissue by up to 40%. Based on these findings, we propose a cholesterol dependent model for COVID19 lethality in elderly and the chronically ill. As cholesterol increases with age and inflammation (e.g. obesity, smoking, and diabetes), the cell surface is coated with viral entry points, optimally assembled viral entry proteins, and optimal furin priming. Importantly our model suggests problems arise when cholesterol levels are high in the tissue, not the blood. In fact, rapidly dropping cholesterol in the blood may indicate severe loading of cholesterol in peripheral tissue and a dangerous situation for escalated SARS-CoV-2 infectivity. Molecules that remove cholesterol from tissue or disrupt ACE2 localization with viral entry points or furin localization for priming in the producer cells, likely reduce the severity of COVID19 in critically ill patients.

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COVID-19: Why it kills the elderly and what we should do about it

BY MATT KAEBERLEIN, OPINION CONTRIBUTOR — 05/17/20 01:00 PM EDT
THE VIEWS EXPRESSED BY CONTRIBUTORS ARE THEIR OWN AND NOT THE VIEW OF THE HILL

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Most of us already recognize that 2020 is a year where everything changed. In just a few months, the COVID-19 pandemic has dramatically impacted the lives of billions of people, many of which will never be the same.

One of the most striking features of COVID-19 is its disproportionate impact on the elderly. Indeed, the first recognized outbreak in the U.S. killed 35 residents at the Life Care Center nursing home in Kirkland, Washington. This occurred in early March after the virus had spread silently in the local population for several weeks, but it was only upon exposure of this vulnerable group that the severity of COVID-19 began to be appreciated. Now only two months later, more than 80,000 Americans and nearly 300,000 people worldwide have succumbed to COVID-19, the majority of these deaths occurring in those over 65.

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Severe COVID-19: A Review of Recent Progress With a Look Toward the Future

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The novel coronavirus disease 2019 (COVID-19) is an acute infectious disease caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Currently, the World Health Organization has confirmed that COVID-19 is a global infectious disease pandemic. This is the third acute infectious disease caused by coronavirus infection in this century, after sudden acute respirator syndrome and Middle East respiratory syndrome. The damage mechanism of SARS-CoV-2 is still unclear. It is possible that protein S binds to angiotensin-converting enzyme 2 receptors and invades alveolar epithelial cells, causing direct toxic effects and an excessive immune response. This stimulates a systemic inflammatory response, thus forming a cytokine storm, which leads to lung tissue injury. In severe cases, the disease can lead to acute respiratory distress syndrome, septic shock, metabolic acidosis, coagulation dysfunction, and multiple organ dysfunction syndromes. Patients with severe COVID-19 have a relatively high mortality rate. Currently, there are no specific antiviral drugs for the treatment of COVID-19. Most patients need to be admitted to the intensive care unit for intensive monitoring and supportive organ function treatments. This article reviews the epidemiology, pathogenesis, clinical manifestations, diagnosis, and treatment methods of severe COVID-19 and puts forward some tentative ideas, aiming to provide some guidance for the diagnosis and treatment of severe COVID-19.

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Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis

Findings

Our search identified 172 observational studies across 16 countries and six continents, with no randomised controlled trials and 44 relevant comparative studies in health-care and non-health-care settings (n=25 697 patients). Transmission of viruses was lower with physical distancing of 1 m or more, compared with a distance of less than 1 m (n=10 736, pooled adjusted odds ratio [aOR] 0·18, 95% CI 0·09 to 0·38; risk difference [RD] −10·2%, 95% CI −11·5 to −7·5; moderate certainty); protection was increased as distance was lengthened (change in relative risk [RR] 2·02 per m; $p_{interaction}$=0·041; moderate certainty). Face mask use could result in a large reduction in risk of infection (n=2647; aOR 0·15, 95% CI 0·07 to 0·34, RD −14·3%, −15·9 to −10·7; low certainty), with stronger associations with N95 or similar respirators compared with disposable surgical masks or similar (eg, reusable 12–16-layer cotton masks; $p_{interaction}$=0·090; posterior probability >95%, low certainty). Eye protection also was associated with less infection (n=3713; aOR 0·22, 95% CI 0·12 to 0·39, RD −10·6%, 95% CI −12·5 to −7·7; low certainty). Unadjusted studies and subgroup and sensitivity analyses showed similar findings.

Interpretation

The findings of this systematic review and meta-analysis support physical distancing of 1 m or more and provide quantitative estimates for models and contact tracing to inform policy. Optimum use of face masks, respirators, and eye protection in public and health-care settings should be informed by these findings and contextual factors. Robust randomised trials are needed to better inform the evidence for these interventions, but this systematic appraisal of currently best available evidence might inform interim guidance.

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Jim Mellon Donates £1 Million to Aging Research

Steve Hill May 18, 2020

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Share

Investment mogul Jim Mellon has donated a record-breaking 1 million British pounds to Oriel College in the United Kingdom, offering a ray of light for aging research.

NIA Caenorhabditis Intervention Testing Program (CITP) Announces a Call for Compounds to Test for Anti-Aging Activity in Caenorhabditis

The National Institute on Aging (NIA) *Caenorhabditis* Interventions Testing Program (CITP) was established to test compounds purported to extend lifespan and/or delay the onset of disease and disability. The NIA CITP aims to identify pharmacological interventions that increase lifespan and/or healthspan in a robust manner using a genetically diverse set of *Caenorhabditis* strains. The CITP is comprised of four major components—three screening centers and a data coordination center. The principal investigators at the three screening centers are (1) Monica Driscoll - Rutgers, The State University of New Jersey; (2) Patrick Phillips - University of Oregon; (3) Gordon Lithgow - Buck Institute. The data coordination center is also headed by Patrick Phillips at University of Oregon.

The NIA CITP is soliciting proposals for compounds to enter the study in 2020-2021. This is not a funding opportunity announcement, but rather a solicitation of nominations for compounds to be tested in the CITP. The first deadline for receipt of proposals is June 30, 2020. Information on the NIA CITP and guidelines for proposal development are posted on the NIA website (to be developed) and the CITP website. Proposals should be submitted electronically to Tracy Cope.

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Due to the COVID-19 pandemic, we're sad to inform you that EHA2020 will be rescheduled to next year. More info will follow.

EHA

Eurosymposium on Healthy Ageing

October 1-3, 2020
Brussels, Belgium

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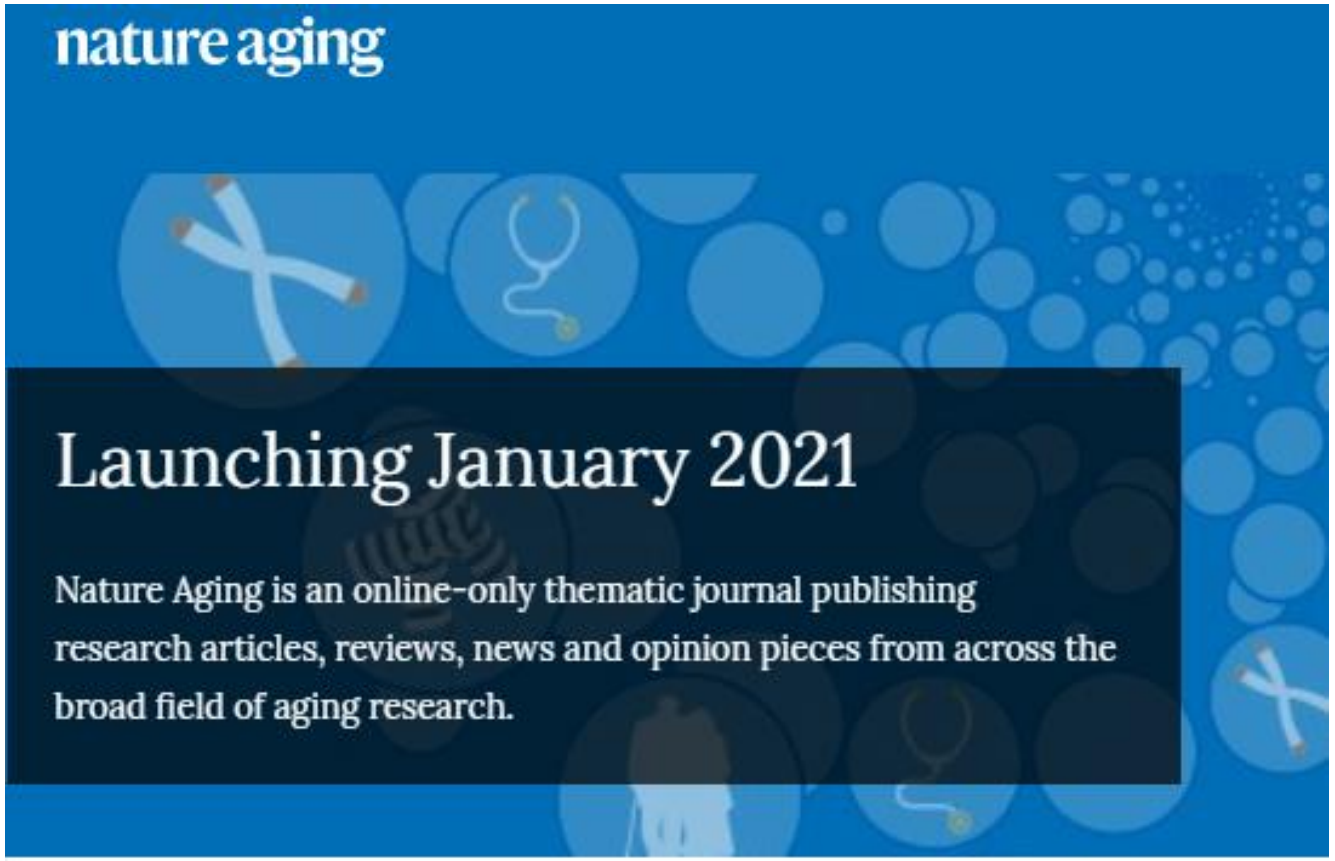

Announcement

Now open for submissions

Nature Aging is now open for submissions.

Announcement

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Aging research articles

Rethinking Morbidity Compression

Rosie Seaman [1 2], Andreas Höhn [3 4 5], Rune Lindahl-Jacobsen [5 6], Pekka Martikainen [3 7], Alyson van Raalte [3], Kaare Christensen [5 8]

Studies of morbidity compression routinely report the average number of years spent in an unhealthy state but do not report variation in age at morbidity onset. Variation was highlighted by Fries (1980) as crucial for identifying disease postponement. Using incidence of first hospitalization after age 60, as one working example, we estimate variation in morbidity onset over a 27-year period in Denmark. Annual estimates of first hospitalization and the population at risk for 1987 to 2014 were identified using population-based registers. Sex-specific life tables were constructed, and the average age, the threshold age, and the coefficient of variation in age at first hospitalization were calculated. On average, first admissions lasting two or more days shifted towards older ages between 1987 and 2014. The average age at hospitalization increased from 67.8 years (95% CI 67.7-67.9) to 69.5 years (95% CI 69.4-69.6) in men, and 69.1 (95% CI 69.1-69.2) to 70.5 years (95% CI 70.4-70.6) in women. Variation in age at first admission increased slightly as the coefficient of variation increased from 9.1 (95% CI 9.0-9.1) to 9.9% (95% CI 9.8-10.0) among men, and from 10.3% (95% CI 10.2-10.4) to 10.6% (95% CI 10.5-10.6) among women. Our results suggest populations are ageing with better health today than in the past, but experience increasing diversity in healthy ageing. Pensions, social care, and health services will have to adapt to increasingly heterogeneous ageing populations, a phenomenon that average measures of morbidity do not capture.

Age-specific cancer rates: a bird's-eye view on progress

Purpose

We aim to shed light on progress in cancer medicine through studying time trends in age-specific rates of cancer incidence and mortality over the last quarter century.

Methods

We analyzed age-specific incidence and mortality rates of all cancer sites combined using the high-quality population-based databases of Denmark, Finland, Norway, Sweden, and the Netherlands for the period 1990–2016.

Results

Over these 26 years, cancer incidence rates increased in all investigated countries irrespective of age by about 22%. By contrast, cancer mortality rates decreased across all ages, also by about 22%, except ages 80+ years in Denmark, Norway, and Sweden, where they remained unchanged. This pattern is consistent with earlier diagnoses and more effective treatments of cancer.

Conclusions

This bird's-eye view on cancer reveals substantive progress in cancer medicine.

Rejuvenation of three germ layers tissues by exchanging old blood plasma with saline-albumin

Melod Mehdipour[1] , Colin Skinner[1, *] , Nathan Wong[1, *] , Michael Lieb[1, *] , Chao Liu[1] , Jessy Etienne[1] , Cameron Kato[1] , Dobri Kiprov[2] , Michael J. Conboy[1] , Irina M. Conboy[1]

Heterochronic blood sharing rejuvenates old tissues, and most of the studies on how this works focus on young plasma, its fractions, and a few youthful systemic candidates. However, it was not formally established that young blood is necessary for this multi-tissue rejuvenation. Here, using our recently developed small animal blood exchange process, we replaced half of the plasma in mice with saline containing 5% albumin (terming it a "neutral" age blood exchange, NBE) thus diluting the plasma factors and replenishing the albumin that would be diminished if only saline was used. Our data demonstrate that a single NBE suffices to meet or exceed the rejuvenative effects of enhancing muscle repair, reducing liver adiposity and fibrosis, and increasing hippocampal neurogenesis in old mice, all the key outcomes seen after blood heterochronicity. Comparative proteomic analysis on serum from NBE, and from a similar human clinical procedure of therapeutic plasma exchange (TPE), revealed a molecular re-setting of the systemic signaling milieu, interestingly, elevating the levels of some proteins, which broadly coordinate tissue maintenance and repair and promote immune responses. Moreover, a single TPE yielded functional blood rejuvenation, abrogating the typical old serum inhibition of progenitor cell proliferation. Ectopically added albumin does not seem to be the sole determinant of such rejuvenation, and levels of albumin do not decrease with age nor are increased by NBE/TPE. A model of action (supported by a large body of published data) is that significant dilution of autoregulatory proteins that crosstalk to multiple signaling pathways (with their own feedback loops) would, through changes in gene expression, have long-lasting molecular and functional effects that are consistent with our observations. This work improves our understanding of the systemic paradigms of multi-tissue rejuvenation and suggest a novel and immediate use of the FDA approved TPE for improving the health and resilience of older people.

Defined $p16^{High}$ Senescent Cell Types Are Indispensable for Mouse Healthspan

The accumulation of senescent cells can drive many age-associated phenotypes and pathologies. Consequently, it has been proposed that removing senescent cells might extend lifespan. Here, we generated two knockin mouse models targeting the best-characterized marker of senescence, $p16^{Ink4a}$. Using a genetic lineage tracing approach, we found that age-induced $p16^{High}$ senescence is a slow process that manifests around 10–12 months of age. The majority of $p16^{High}$ cells were vascular endothelial cells mostly in liver sinusoids (LSECs), and to lesser extent macrophages and adipocytes. In turn, continuous or acute elimination of $p16^{High}$ senescent cells disrupted blood-tissue barriers with subsequent liver and perivascular tissue fibrosis and health deterioration. Our data show that senescent LSECs are not replaced after removal and have important structural and functional roles in the aging organism. In turn, delaying senescence or replacement of senescent LSECs could represent a powerful tool in slowing down aging.

Mitochondria-Targeting Plasmonic Spiky Nanorods Increase the Elimination of Aging Cells in Vivo

Cellular senescence is stress-induced, irreversible growth arrest, and is thought to impair tissue function. The clearance of senescent cells can delay the features of senescence. Herein, we report the development of plasmonic core–shell spiky nanorods (CSNRs) surface-modified with an anti-beta-2-microglobulin (aB2MG) antibody and triphenylphosphonium (TPP), to target the mitochondria in senescent cells. aB2MG-TPP@CSNRs irradiated with near-infrared (NIR) light selectively caused mitochondrial damage and apoptosis of senescent cells with relatively low NIR light power, and the ability of CSNRs to activate and amplify the immune response in vitro and in vivo was discovered. The photo-induced generation of reactive oxygen species (ROS) resulted in senescent-cell apoptosis and immune adjuvant effect by CSNRs accelerated the clearance of senescent cells in mice. This study opens the way for the use of precisely regulated plasmonic nanostructures for immune adjuvant and photo-induced apoptosis for age-related senescence.

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Effect of senolytic treatment on expression of senescence-associated miR-126 expression in young and old female mice.

Cellular senescence represents one of the major risk factors for chronic liver disease and contributes to morbidity, mortality, and increased healthcare spending. A relevant strategy for understanding the role of senescent cells in liver pathogenesis is to use genetic or pharmacological strategies to eliminate senescent cells. The combination of the senolytic drugs, Dasatinib and Quercetin (D+Q), effectively reduces senescent cell burden in multiple tissues, extending both healthspan and lifespan in mice, and alliviating obesity and age-associated hepatic steatosis. The aim of this study was to investigate effects of D+Q treatment on livers of young and old female mice. A total of 40 mice, 20 young females (3-months) and 20 old females (18-months), was divided into 4 groups: Young (Y) mice treated with either D+Q or placebo and old (O) mice treated with D+Q or placebo. The treatment was performed for 3 consecutive days every 2 weeks over 10 weeks. Comparative analysis of hepatic miRNAs indicated that D+Q treatment significantly decreased levels of senescence-specific miR-126 expression in livers of old mice treated with D+Q compared to vehicle-treated old mice ($p=0.025$), As expected, there was no effect of D+Q treatment in young animals. Analysis of miR-126 target genes indicated that PI3K gene expression was significantly increased in response to D+Q treatment ($p=0.003$). Additionally, Akt1 and mTOR mRNA levels were increased in D+Q-treated mice ($p=0.008$ and $p=0.02$, respectively). In summary, our data suggest that the mechanism of PI3K signaling pathway activation upon elimination of senescent cells by treatment with D+Q is mediated through downregulation of senescence-specific miR-126.

Opposing p53 and mTOR/AKT promote an in vivo switch from apoptosis to senescence upon telomere shortening in zebrafish

Progressive telomere shortening during lifespan is associated with restriction of cell proliferation, genome instability and aging. Apoptosis and senescence are the two major outcomes upon irreversible cellular damage. Here, we show a transition of these two cell fates during aging of telomerase deficient zebrafish. In young telomerase mutants, proliferative tissues exhibit DNA damage and p53-dependent apoptosis, but no senescence. However, these tissues in older animals display loss of cellularity and senescence becomes predominant. Tissue alterations are accompanied by a pro-proliferative stimulus mediated by AKT signaling. Upon AKT activation, FoxO transcription factors are phosphorylated and translocated out of the nucleus. This results in reduced SOD2 expression causing an increase of ROS and mitochondrial dysfunction. These alterations induce p15/16 growth arrest and senescence. We propose that, upon telomere shortening, early apoptosis leads to cell depletion and insufficient compensatory proliferation. Following tissue damage, the mTOR/AKT is activated causing mitochondrial dysfunction and p15/16-dependent senescence.

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A CellAgeClock for expedited discovery of anti-ageing compounds

We aim to improve anti-ageing drug discovery, currently achieved through laborious and lengthy longevity analysis. Recent studies demonstrated that the most accurate molecular method to measure human age is based on CpG methylation profiles, as exemplified by several epigenetics clocks that can accurately predict an individual's age. Here, we developed CellAgeClock, a new epigenetic clock that measures subtle ageing changes in primary human cells *in vitro*. As such, it provides a unique tool to measure effects of relatively short pharmacological treatments on ageing. We validated the CellAgeClock against known longevity drugs such as rapamycin and trametinib. Moreover, we uncovered novel anti-ageing drugs, torin2 and Dactolisib (BEZ-235), demonstrating the value of our approach as a screening and discovery platform for anti-ageing strategies. The CellAgeClock outperforms other epigenetic clocks in measuring subtle ageing changes in primary human cells in culture. The tested drug treatments reduced senescence and other ageing markers, further consolidating our approach as a screening platform. Finally, we show that the novel anti-ageing drugs we uncovered *in vitro*, indeed increased longevity *in vivo*. Our method expands the scope of CpG methylation profiling from measuring human chronological and biological age from human samples in years, to accurately and rapidly detecting anti-ageing potential of drugs using human cells *in vitro*, providing a novel accelerated discovery platform to test sought after geroprotectors.

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Reversing age: dual species measurement of epigenetic age with a single clock

Abstract

Young blood plasma is known to confer beneficial effects on various organs in mice. However, it was not known whether young plasma rejuvenates cells and tissues at the epigenetic level; whether it alters the epigenetic clock, which is a highly-accurate molecular biomarker of aging. To address this question, we developed and validated six different epigenetic clocks for rat tissues that are based on DNA methylation values derived from n=593 tissue samples. As indicated by their respective names, the rat pan-tissue clock can be applied to DNA methylation profiles from all rat tissues, while the rat brain-, liver-, and blood clocks apply to the corresponding tissue types. We also developed two epigenetic clocks that apply to both human and rat tissues by adding n=850 human tissue samples to the training data. We employed these six clocks to investigate the rejuvenation effects of a plasma fraction treatment in different rat tissues. The treatment more than halved the epigenetic ages of blood, heart, and liver tissue. A less pronounced, but statistically significant, rejuvenation effect could be observed in the hypothalamus. The treatment was accompanied by progressive improvement in the function of these organs as ascertained through numerous biochemical/physiological biomarkers and behavioral responses to assess cognitive functions. Cellular senescence, which is not associated with epigenetic aging, was also considerably reduced in vital organs. Overall, this study demonstrates that a plasma-derived treatment markedly reverses aging according to epigenetic clocks and benchmark biomarkers of aging.

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A rat epigenetic clock recapitulates phenotypic aging and co-localizes with heterochromatin-associated histone modifications

Aging has been shown to be a strong driver of DNA methylation changes, leading to the development of robust biomarkers in humans and more recently, in mice. This study aimed to generate a novel epigenetic clock in rats—a model with unique physical, physiological, and biochemical advantages for studying mammalian aging. Additionally, we incorporated behavioral data, unsupervised machine learning, and network analysis to identify epigenetic signals that not only track with age, but also relate to phenotypic aging and reflect higher-order molecular aging changes. We used DNAm data from reduced representation bisulfite sequencing (RRBS) to train an epigenetic age (DNAmAge) measure in Fischer 344 CDF (F344) rats. In an independent sample of n=32 F344 rats, we found that this measure correlated with age at (r=0.93), and related to physical functioning (5.9e-3), after adjusting for age and differential cell counts. DNAmAge was also found to correlate with age in C57BL/6 mice (r=0.79), and was decreased in response to caloric restriction (CR), such that the longer the animal was on a CR diet, the greater the decrease in DNAm. We also observed resetting of DNAm when kidney and lung fibroblasts when converted to induced pluripotent stem cells (iPSCs). Using weighted gene correlation network analysis (WGCNA) we identified two modules that appeared to drive our DNAmAge measure. These two modules contained CpGs in intergenic regions that showed substantial overlap with histone marks H3K9me3, H3K27me3, and E2F1 transcriptional factor binding. In moving forward, our ability to unravel the complex signals linking DNA methylation changes to functional aging would require experimental studies in model systems in which longitudinal epigenetic changes can be related to other molecular and physiological hallmarks of aging.

Quantification of the pace of biological aging in humans through a blood test, The DunedinPoAm DNA methylation algorithm

Biological aging is the gradual, progressive decline in system integrity that occurs with advancing chronological age, causing morbidity and disability. Measurements of the pace of aging are needed as surrogate endpoints in trials of therapies designed to prevent disease by slowing biological aging. We report a blood-DNA-methylation measure that is sensitive to variation in pace of biological aging among individuals born the same year. We first modeled change-over-time in 18 biomarkers tracking organ-system integrity across 12 years of follow-up in n=954 members of the Dunedin Study born in 1972-1973. Rates of change in each biomarker over ages 26-38 years were composited to form a measure of aging-related decline, termed Pace-of-Aging. Elastic-net regression was used to develop a DNA-methylation predictor of Pace-of-Aging, called DunedinPoAm for Dunedin(P)ace(o)f(A)ging(m)ethylation. Validation analysis in cohort studies and the CALERIE trial provide proof-of-principle for DunedinPoAm as a single-time-point measure of a person's pace of biological aging.

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Epigenetic aging of classical monocytes from healthy individuals

The impact of healthy aging on molecular programming of immune cells is poorly understood. Here, we report comprehensive characterization of healthy aging in human classical monocytes, with a focus on epigenomic, transcriptomic, and proteomic alterations, as well as the corresponding proteomic and metabolomic data for plasma, using healthy cohorts of 20 young and 20 older individuals (~27 and ~64 years old on average). For each individual, we performed eRRBS-based DNA methylation profiling, which allowed us to identify a set of age-associated differentially methylated regions (DMRs) – a novel, cell-type specific signature of aging in DNA methylome. Optimized ultra-low-input ChIP-seq (ULI-ChIP-seq) data acquisition and analysis pipelines applied to 5 chromatin marks for each individual revealed lack of large-scale age-associated changes in chromatin modifications and allowed us to link hypo- and hypermethylated DMRs to distinct chromatin modification patterns. Specifically, hypermethylation events were associated with H3K27me3 in the CpG islands near promoters of lowly-expressed genes, while hypomethylated DMRs were enriched in H3K4me1 marked regions and associated with normal pattern of expression. Furthermore, hypo- and hypermethylated DMRs followed distinct functional and genetic association patterns. Hypomethylation events were associated with age-related increase of expression of the corresponding genes, providing a link between DNA methylation and age-associated transcriptional changes in primary human cells. Furthermore, these locations were also enriched in genetic regions associated by GWAS with asthma, total blood protein, hemoglobin levels and MS. On the other side, acceleration of epigenetic age in HIV and asthma stems only from changes in hypermethylated DMRs but not from hypomethylated loci.

Metformin Enhances Autophagy and Normalizes Mitochondrial Function to Alleviate Aging–Associated Inflammation

Age is a non-modifiable risk factor for the inflammation that underlies age-associated diseases; thus, anti-inflammaging drugs hold promise for increasing health span. Cytokine profiling and bioinformatic analyses showed that Th17 cytokine production differentiates $CD4^+$ T cells from lean, normoglycemic older and younger subjects, and mimics a diabetes-associated Th17 profile. T cells from older compared to younger subjects also had defects in autophagy and mitochondrial bioenergetics that associate with redox imbalance. Metformin ameliorated the Th17 inflammaging profile by increasing autophagy and improving mitochondrial bioenergetics. By contrast, autophagy-targeting siRNA disrupted redox balance in T cells from young subjects and activated the Th17 profile by activating the Th17 master regulator, STAT3, which in turn bound IL-17A and F promoters. Mitophagy-targeting siRNA failed to activate the Th17 profile. We conclude that metformin improves autophagy and mitochondrial function largely in parallel to ameliorate a newly defined inflammaging profile that echoes inflammation in diabetes.

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

Genetic predisposition is believed to contribute substantially to the age at which we die. Genome-wide association studies (GWAS) have implicated more than 20 genetic 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 238,239 UK Biobank participants, we assessed the relevance of protein-truncating variant (PTV) gene burden on individual and parental survival. We identified exome-wide (P<2.5e-6) significant associations between *BRCA2*, *BRCA1*, *TET2*, *PPM1D*, *LDLR*, *EML2* and *DEDD2* PTV-burden with human lifespan. Gene and gene-set PTV-burden phenome-wide association studies (PheWAS) further highlighted the roles of these genes in cancer and cardiovascular disease as relevant for overall survival. The overlap between PTV-burden and prior GWAS results was modest, underscoring the value of sequencing in well-powered cohorts to complement GWAS for identifying loci associated with complex traits and disease.

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GWAS for Lifespan and Decline in Climbing Ability in Flies upon Dietary Restriction Reveal *decima* as a Mediator of Insulin-like Peptide Production

Dietary restriction (DR) is the most robust means to extend lifespan and delay age-related diseases across species. An underlying assumption in the aging field is that DR enhances both lifespan and physical activity through similar mechanisms, but this has not been rigorously tested in different genetic backgrounds. Furthermore, nutrient response genes responsible for lifespan extension or age-related decline in functionality remain underexplored in natural populations. To address this, we measured nutrient-dependent changes in lifespan and age-related decline in climbing ability in the *Drosophila* Genetic Reference Panel fly strains. On average, DR extended lifespan and delayed decline in climbing ability, but there was a lack of correlation between these traits across individual strains, suggesting that distinct genetic factors modulate these traits independently and that genotype determines response to diet. Only 50% of strains showed positive response to DR for both lifespan and climbing ability, 14% showed a negative response for one trait but not both, and 35% showed no change in one or both traits. Through GWAS, we uncovered a number of genes previously not known to be diet responsive nor to influence lifespan or climbing ability. We validated *decima* as a gene that alters lifespan and *daedalus* as one that influences age-related decline in climbing ability. We found that *decima* influences insulin-like peptide transcription in the GABA receptor neurons downstream of *short neuropeptide F precursor* (*sNPF*) signaling. Modulating these genes produced independent effects on lifespan and physical activity decline, which suggests that these age-related traits can be regulated through distinct mechanisms.

Are We Approaching a Biological Limit to Human Longevity?

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The Journals of Gerontology: Series A, Volume 75, Issue 6, June 2020, Pages 1061–1067,
https://doi.org/10.1093/gerona/glz164
Published: 04 June 2019 **Article history** ▾

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Abstract

Until recently human longevity records continued to grow in history, with no indication of approaching a hypothetical longevity limit. Also, earlier studies found that age-specific death rates cease to increase at advanced ages (mortality plateau) suggesting the absence of fixed limit to longevity too. In this study, we reexamine both claims with more recent and reliable data on supercentenarians (persons aged 110 years and older). We found that despite a dramatic historical increase in the number of supercentenarians, further growth of human longevity records in subsequent birth cohorts slowed down significantly and almost stopped for those born after 1879. We also found an exponential acceleration of age-specific death rates for persons older than 113 years in more recent data. Slowing down the historical progress in maximum reported age at death and accelerated growth of age-specific death rates after age 113 years in recent birth cohorts may indicate the need for more conservative estimates for future longevity records unless a scientific breakthrough in delaying aging would happen. The hypothesis of approaching a biological limit to human longevity has received some empirical support and it deserves further study and testing.

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Spread of pathological tau proteins through communicating neurons in human Alzheimer's disease

Tau is a hallmark pathology of Alzheimer's disease, and animal models have suggested that tau spreads from cell to cell through neuronal connections, facilitated by β-amyloid (Aβ). We test this hypothesis in humans using an epidemic spreading model (ESM) to simulate tau spread, and compare these simulations to observed patterns measured using tau-PET in 312 individuals along Alzheimer's disease continuum. Up to 70% of the variance in the overall spatial pattern of tau can be explained by our model. Surprisingly, the ESM predicts the spatial patterns of tau irrespective of whether brain Aβ is present, but regions with greater Aβ burden show greater tau than predicted by connectivity patterns, suggesting a role of Aβ in accelerating tau spread. Altogether, our results provide evidence in humans that tau spreads through neuronal communication pathways even in normal aging, and that this process is accelerated by the presence of brain Aβ.

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Innate and Adaptive Immunity in Aging and Longevity: The Foundation of Resilience

Moskalev Alexey[1,*], Stambler Ilia[2,*], Caruso Calogero[3,*]

The interrelation of the processes of immunity and senescence now receives an unprecedented emphasis during the COVID-19 pandemic, which brings to the fore the critical need to combat immunosenescence and improve the immune function and resilience of older persons. Here we review the historical origins and the current state of the science of innate and adaptive immunity in aging and longevity. From the modern point of view, innate and adaptive immunity are not only affected by aging but also are important parts of its underlying mechanisms. Excessive levels or activity of antimicrobial peptides, C-reactive protein, complement system, TLR/NF-κB, cGAS/STING/IFN 1,3 and AGEs/RAGE pathways, myeloid cells and NLRP3 inflammasome, declined levels of NK cells in innate immunity, thymus involution and decreased amount of naive T-cells in adaptive immunity, are biomarkers of aging and predisposition factors for cellular senescence and aging-related pathologies. Long-living species, human centenarians, and women are characterized by less inflamm-aging and decelerated immunosenescence. Despite recent progress in understanding, the harmonious theory of immunosenescence is still developing. Geroprotectors targeting these mechanisms are just emerging and are comprehensively discussed in this article.

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Autophagy in T cells from aged donors is maintained by spermidine, and correlates with function and vaccine responses

Older adults are at high risk for infectious diseases such as the recent COVID-19 and vaccination seems to be the only long-term solution to the pandemic. While most vaccines are less efficacious in older adults, little is known about the molecular mechanisms that underpin this. Autophagy, a major degradation pathway and one of the few processes known to prevent aging, is critical for the maintenance of immune memory in mice. Here, we show induction of autophagy is specifically induced in human vaccine-induced antigen-specific T cells *in vivo*. Reduced IFNγ secretion by vaccine-induced T cells in older vaccinees correlates with low autophagy. We demonstrate in human cohorts that levels of the endogenous autophagy-inducing metabolite spermidine, fall with age and supplementing it *in vitro* recovers autophagy and T cell function. Finally, our data show that endogenous spermidine maintains autophagy via the translation factor eIF5A and transcription factor TFEB. With these findings we have uncovered novel targets and biomarkers for the development of anti-aging drugs for human T cells, providing evidence for the use of spermidine in improving vaccine immunogenicity in the aged human population.

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Fibroblast rejuvenation by mechanical reprogramming and redifferentiation

Over the course of the aging process, fibroblasts lose contractility, leading to reduced connective-tissue stiffness. A promising therapeutic avenue for functional rejuvenation of connective tissue is reprogrammed fibroblast replacement, although major hurdles still remain. Toward this, we recently demonstrated that the laterally confined growth of fibroblasts on micropatterned substrates induces stem-cell-like spheroids. In this study, we embedded these partially reprogrammed spheroids in collagen-I matrices of varying densities, mimicking different three-dimensional (3D) tissue constraints. In response to such matrix constraints, these spheroids regained their fibroblastic properties and sprouted to form 3D connective-tissue networks. Interestingly, we found that these differentiated fibroblasts exhibit reduced DNA damage, enhanced cytoskeletal gene expression, and actomyosin contractility. In addition, the rejuvenated fibroblasts show increased matrix protein (fibronectin and laminin) deposition and collagen remodeling compared to the parental fibroblast tissue network. Furthermore, we show that the partially reprogrammed cells have comparatively open chromatin compaction states and may be more poised to redifferentiate into contractile fibroblasts in 3D-collagen matrix. Collectively, our results highlight efficient fibroblast rejuvenation through laterally confined reprogramming, which has important implications in regenerative medicine.

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Comparative Blood and Urine Metabolomics Analysis of Healthy Elderly and Young Male Singaporeans

Comparative metabolomics analysis of biofluids could provide information about the metabolic alterations in aging. To investigate the signature of multiple metabolic profiles associated with aging in an Asian population, we performed a pilot study in healthy Singaporeans, including 33 elderly and 33 young males. Fasting whole bloods were analyzed by routine hematology; the serum and urine metabolome profiles were obtained using NMR-based nontargeted metabolomics analysis and targeted lipoprotein analysis. Among the 90 identified compounds in serum and urine samples, 32 were significantly different between the two groups. The most obvious age-related metabolic signatures include decreased serum levels of albumin lysyl and essential amino acids and derivatives but increased levels of *N*-acetyl glycoproteins and several lipids and elevated urine levels of trimethylamine *N*-oxide, *scyllo*-inositol, citrate, and ascorbic acid but decreased levels of several amino acids, acetate, etc. Among 112 lipoprotein subfractions, 65 were elevated, and 2 were lower in the elderly group. These significantly age-varying metabolites, especially in the amino acid and fatty acid metabolism pathways, suggest that the regulation of these pathways contributes to the aging process in Chinese Singaporeans. Further multiomics studies including the gut microbiome and intervention studies in a larger cohort are needed to elucidate the possible mechanisms in the aging process.

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Age-related Compositional Changes and Correlations of Gut Microbiome, Serum Metabolome, and Immune Factor in Rats

Aging is a complex physiological process associated with degenerative disorder of metabolism and immune function, which contributes to the occurrence of senile diseases. The gut microbiota affects systemic inflammation in aging processes probably through metabolism, but their relationship is still unclear. In this study, 16S-rRNA-sequencing technology, gas chromatography-time-of-flight mass spectrometry (GC-TOFMS)-based metabolic profiling, and immune factor analysis combined with advanced differential and association analysis were employed to investigate the correlation between the microbiome, metabolome, and immune factors in male Wistar rats across lifespan. Our findings showed significant changes in the ileum microbiome and serum metabolome compositions across aging process. A two-level strategy was applied to demonstrate that key metabolites associated with age such as 4-hydroxyproline, proline, and lysine were clustered together and positively correlated with beneficial microbes including Bifidobacterium, Lactobacillus, and Akkermansia. Function analysis explored association between serum metabolite class and specific gut bacteria's metabolism pathways. Further correlation analysis on all the alteration patterns provided an interaction network of main immune factors such as IL-10, IgA, IgM, and IgG with key gut bacteria and serum metabolites. This study offers new insights into the relationship between immune factors, serum metabolome, and the gut microbiome.

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Low abundance of NDUFV2 and NDUFS4 subunits of the hydrophilic complex I domain and VDAC1 predicts mammalian longevity

Mitochondrial reactive oxygen species (ROS) production, specifically at complex I (Cx I), has been widely suggested to be one of the determinants of species longevity. The present study follows a comparative approach to analyse complex I in heart tissue from 8 mammalian species with a longevity ranging from 3.5 to 46 years. Gene expression and protein content of selected Cx I subunits were analysed using droplet digital PCR (ddPCR) and western blot, respectively. Our results demonstrate: 1) the existence of species-specific differences in gene expression and protein content of Cx I in relation to longevity; 2) the achievement of a longevity phenotype is associated with low protein abundance of subunits NDUFV2 and NDUFS4 from the matrix hydrophilic domain of Cx I; and 3) long-lived mammals show also lower levels of VDAC (voltage-dependent anion channel) amount. These differences could be associated with the lower mitochondrial ROS production and slower aging rate of long-lived animals and, unexpectedly, with a low content of the mitochondrial permeability transition pore in these species.

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Naked mole-rat very-high-molecular-mass hyaluronan exhibits superior cytoprotective properties

Naked mole-rat (NMR), the longest-living rodent, produces very-high-molecular-mass hyaluronan (vHMM-HA), compared to other mammalian species. However, it is unclear if exceptional polymer length of vHMM-HA is important for longevity. Here, we show that vHMM-HA (>6.1 MDa) has superior cytoprotective properties compared to the shorter HMM-HA. It protects not only NMR cells, but also mouse and human cells from stress-induced cell-cycle arrest and cell death in a polymer length-dependent manner. The cytoprotective effect is dependent on the major HA-receptor, CD44. We find that vHMM-HA suppresses CD44 protein-protein interactions, whereas HMM-HA promotes them. As a result, vHMM-HA and HMM-HA induce opposing effects on the expression of CD44-dependent genes, which are associated with the p53 pathway. Concomitantly, vHMM-HA partially attenuates p53 and protects cells from stress in a p53-dependent manner. Our results implicate vHMM-HA in anti-aging mechanisms and suggest the potential applications of vHMM-HA for enhancing cellular stress resistance.

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Health benefits attributed to 17α-estradiol, a lifespan-extending compound, are mediated through estrogen receptor α

Aging is the greatest risk factor for most chronic diseases. Metabolic dysfunction underlies several chronic diseases, which are further exacerbated by obesity. Dietary interventions can reverse metabolic declines and slow aging processes, although compliance issues remain paramount due to adverse effects on quality of life. 17α-estradiol treatment improves metabolic parameters and slows aging in male mice. The mechanism by which 17α-E2 elicits benefits remain unknown, which has led speculation that an uncharacterized receptor is involved. Herein, we show that 17α-estradiol and 17β-estradiol elicit similar genomic binding and transcriptional activation of ERα and that the ablation of ERα in male mice completely attenuates the beneficial effects of 17α-estradiol. Our findings also suggest that 17α-E2 acts primarily through the liver and/or hypothalamus to elicit benefits, and that 17α-E2 also improves metabolic parameters in male rats. Collectively, these data suggest ERα is a relevant drug target for mitigating chronic diseases in male mammals.

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The changes in the p53 protein across the animal kingdom pointing to its involvement in longevity

Recently, the quest for the mythical fountain of youth has turned into specific research programs aiming to extend the healthy lifespan of humans. Despite advances in our understanding of the molecular processes underlying aging, the surprisingly extended lifespan of some animals remains unexplained. In this respect, the p53 protein plays a crucial role not only in tumor suppression but also in tissue homeostasis and healthy aging. However, the mechanism through which p53 maintains the function as a gatekeeper of healthy aging is not fully understood. Thus, we inspected *TP*53 gene sequences in individual species of phylogenetically related organisms that show different aging patterns. We discovered novel correlations between specific amino acid variations in p53 and lifespan across different animal species. In particular, we found that species with extended lifespan have characteristic amino acid substitutions mainly in the p53 DNA binding domain that change its function. These findings lead us to propose a theory of longevity based on alterations in *TP53* that might be responsible for determining extended organismal lifespan.

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Glutathione peroxidase-1 overexpression reduces oxidative stress, and improves pathology and proteome remodeling in the kidneys of old mice

This study investigated the direct roles of hydrogen peroxide (H_2O_2) in kidney aging using transgenic mice overexpressing glutathione peroxidase-1 (GPX1 TG). We demonstrated that kidneys in old mice recapitulated kidneys in elderly humans and were characterized by glomerulosclerosis, tubular atrophy, interstitial fibrosis, and loss of cortical mass. Scavenging H_2O_2 by GPX1 TG significantly reduced mitochondrial and total cellular reactive oxygen species (ROS) and mitigated oxidative damage, thus improving these pathologies. The potential mechanisms by which ROS are increased in the aged kidney include a decreased abundance of an anti-aging hormone, Klotho, in kidney tissue, and decreased expression of nuclear respiratory factor 2 (Nrf2), a master regulator of the stress response. Decreased Klotho or Nrf2 was not improved in the kidneys of old GPX1 TG mice, even though mitochondrial morphology was better preserved. Using laser capture microdissection followed by label-free shotgun proteomics analysis, we show that the glomerular proteome in old mice was characterized by decreased abundance of cytoskeletal proteins (critical for maintaining normal glomerular function) and heat shock proteins, leading to increased accumulation of apolipoprotein E and inflammatory molecules. Targeted proteomic analysis of kidney tubules from old mice showed decreased abundance of fatty acid oxidation enzymes and antioxidant proteins, as well as increased abundance of glycolytic enzymes and molecular chaperones. GPX1 TG partially attenuated the remodeling of glomerular and tubule proteomes in aged kidneys. In summary, mitochondria from GPX1 TG mice are protected and kidney aging is ameliorated via its antioxidant activities, independent and downstream of Nrf2 or Klotho signaling.

Untangling Determinants of Enhanced Health and Lifespan Through a Multi-omics Approach in Mice

The impact of chronic caloric restriction (CR) on health and survival is complex with poorly understood underlying molecular mechanisms. A recent study in mice addressing the diets used in nonhuman primate CR studies found that while diet composition did not impact longevity, fasting time and total calorie intake were determinant for increased survival. Here, integrated analysis of physiological and multi-omics data from ad libitum, meal-fed, or CR animals was used to gain insight into pathways associated with improved health and survival. We identified a potential involvement of the glycine-serine-threonine metabolic axis in longevity and related molecular mechanisms. Direct comparison of the different feeding strategies unveiled a pattern of shared pathways of improved health that included short-chain fatty acids and essential PUFA metabolism. These findings were recapitulated in the serum metabolome from nonhuman primates. We propose that the pathways identified might be targeted for their potential role in healthy aging.

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The neuronal receptor tyrosine kinase Alk is a target for longevity

Inhibition of signalling through several receptor tyrosine kinases (RTKs), including the insulin-like growth factor receptor and its orthologues, extends healthy lifespan in organisms from diverse evolutionary taxa. This raises the possibility that other RTKs, including those already well studied for their roles in cancer and developmental biology, could be promising targets for extending healthy lifespan. Here, we focus on anaplastic lymphoma kinase (Alk), an RTK with established roles in nervous system development and in multiple cancers, but whose effects on aging remain unclear. We find that several means of reducing Alk signalling, including mutation of its ligand jelly belly (jeb), RNAi knock-down of Alk, or expression of dominant-negative Alk in adult neurons, can extend healthy lifespan in female, but not male, *Drosophila* . Moreover, reduced Alk signalling preserves neuromuscular function with age, promotes resistance to starvation and xenobiotic stress, and improves night sleep consolidation. We find further that inhibition of Alk signalling in adult neurons modulates the expression of several insulin-like peptides, providing a potential mechanistic link between neuronal Alk signalling and organism-wide insulin-like signalling. Finally, we show that TAE-684, a small molecule inhibitor of Alk, can extend healthy lifespan in *Drosophila* , suggesting that the repurposing of Alk inhibitors may be a promising direction for strategies to promote healthy aging.

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Determinants of accelerated metabolomic and epigenetic aging in a UK cohort

Markers of biological aging have potential utility in primary care and public health. We developed a model of age based on untargeted metabolic profiling across multiple platforms, including nuclear magnetic resonance spectroscopy and liquid chromatography–mass spectrometry in urine and serum, within a large sample (*N* = 2,239) from the UK Airwave cohort. We validated a subset of model predictors in a Finnish cohort including repeat measurements from 2,144 individuals. We investigated the determinants of accelerated aging, including lifestyle and psychological risk factors for premature mortality. The metabolomic age model was well correlated with chronological age (mean *r* = .86 across independent test sets). Increased metabolomic age acceleration (mAA) was associated after false discovery rate (FDR) correction with overweight/obesity, diabetes, heavy alcohol use and depression. DNA methylation age acceleration measures were uncorrelated with mAA. Increased DNA methylation phenotypic age acceleration (*N* = 1,110) was associated after FDR correction with heavy alcohol use, hypertension and low income. In conclusion, metabolomics is a promising approach for the assessment of biological age and appears complementary to established epigenetic clocks.

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A single-cell transcriptomic landscape of primate arterial aging

Our understanding of how aging affects the cellular and molecular components of the vasculature and contributes to cardiovascular diseases is still limited. Here we report a single-cell transcriptomic survey of aortas and coronary arteries in young and old cynomolgus monkeys. Our data define the molecular signatures of specialized arteries and identify eight markers discriminating aortic and coronary vasculatures. Gene network analyses characterize transcriptional landmarks that regulate vascular senility and position FOXO3A, a longevity-associated transcription factor, as a master regulator gene that is downregulated in six subtypes of monkey vascular cells during aging. Targeted inactivation of FOXO3A in human vascular endothelial cells recapitulates the major phenotypic defects observed in aged monkey arteries, verifying FOXO3A loss as a key driver for arterial endothelial aging. Our study provides a critical resource for understanding the principles underlying primate arterial aging and contributes important clues to future treatment of age-associated vascular disorders.

C. elegans aging research

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A transcriptome based aging clock near the theoretical limit of accuracy

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doi: https://doi.org/10.1101/2020.05.29.123430

Abstract

Aging clocks dissociate biological from chronological age. The estimation of biological age is important for identifying gerontogenes and assessing environmental, nutritional or therapeutic impacts on the aging process. Recently, methylation markers were shown to allow estimation of biological age based on age-dependent somatic epigenetic alterations. However, DNA methylation is absent in some species such as *Caenorhabditis elegans* and it remains unclear whether and how the epigenetic clocks affect gene expression. Aging clocks based on transcriptomes have suffered from considerable variation in the data and relatively low accuracy. Here, we devised an approach that uses temporal scaling and binarization of *C. elegans* transcriptomes to define a gene set that predicts biological age with an accuracy that is close to the theoretical limit. Our model accurately predicts the longevity effects of diverse strains, treatments and conditions. The involved genes support a role of specific transcription factors as well as innate immunity and neuronal signaling in the regulation of the aging process. We show that this transcriptome clock can also be applied to human age prediction with high accuracy. This transcriptome aging clock could therefore find wide application in genetic, environmental and therapeutic interventions in the aging process.

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Assessing motor-related phenotypes of *Caenorhabditis elegans* with the wide field-of-view nematode tracking platform

Caenorhabditis elegans is a valuable model organism in biomedical research that has led to major discoveries in the fields of neurodegeneration, cancer and aging. Because movement phenotypes are commonly used and represent strong indicators of *C. elegans* fitness, there is an increasing need to replace manual assessments of worm motility with automated measurements to increase throughput and minimize observer biases. Here, we provide a protocol for the implementation of the improved wide field-of-view nematode tracking platform (WF-NTP), which enables the simultaneous analysis of hundreds of worms with respect to multiple behavioral parameters. The protocol takes only a few hours to complete, excluding the time spent culturing *C. elegans*, and includes (i) experimental design and preparation of samples, (ii) data recording, (iii) software management with appropriate parameter choices and (iv) post-experimental data analysis. We compare the WF-NTP with other existing worm trackers, including those having high spatial resolution. The main benefits of WF-NTP relate to the high number of worms that can be assessed at the same time on a whole-plate basis and the number of phenotypes that can be screened for simultaneously.

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AMPK-mediated Formation of Stress Granules Is Required for Dietary Restriction-Induced Longevity in Caenorhabditis Elegans

Stress granules (SGs) are nonmembranous organelles that are dynamically assembled and disassembled in response to various stressors. Under stressed conditions, polyadenylated mRNAs and translation factors are sequestrated in SGs to promote global repression of protein synthesis. It has been previously demonstrated that SG formation enhances cell survival and stress resistance. However, the physiological role of SGs in organismal aging and longevity regulation remains unclear. In this study, we used TIAR-1::GFP and GTBP-1::GFP as markers to monitor the formation of SGs in Caenorhabditis elegans. We found that, in addition to acute heat stress, SG formation could also be triggered by dietary changes, such as starvation and dietary restriction (DR). We found that HSF-1 is required for the SG formation in response to acute heat shock and starvation but not DR, whereas the AMPK-eEF2K signaling is required for starvation and DR-induced SG formation but not heat shock. Moreover, our data suggest that this AMPK-eEF2K pathway-mediated SG formation is required for lifespan extension by DR, but dispensable for the longevity by reduced insulin/IGF-1 signaling. Collectively, our findings unveil a novel role of SG formation in DR-induced longevity.

A Cellular Surveillance and Defense System That Delays Aging Phenotypes in *C. elegans*

Physiological stresses, such as pathogen infection, are detected by "cellular Surveillance Activated Detoxification and Defenses" (cSADD) systems that trigger host defense responses. Aging is associated with physiological stress, including impaired mitochondrial function. Here, we investigated whether an endogenous cSADD pathway is activated during aging in *C. elegans*. We provide evidence that the transcription factor ZIP-2, a well-known immune response effector in *C. elegans*, is activated in response to age-associated mitochondrial dysfunction. ZIP-2 mitigates multiple aging phenotypes, including mitochondrial disintegration and reduced motility of the pharynx and intestine. Importantly, our data suggest that ZIP-2 is activated during aging independently of bacterial infection and of the transcription factors ATFS-1 and CEBP-2. Thus, ZIP-2 is a key component of an endogenous pathway that delays aging phenotypes in *C. elegans*. Our data suggest that aging coopted a compensatory strategy for regulation of aging process as a guarded process rather than a simple passive deterioration process.

A Feedforward Loop Governs The Relationship Between Lipid Metabolism And Longevity

The relationship between lipid metabolism and longevity remains unclear. In particular although fat oxidation is essential for weight loss, whether it is remains beneficial when sustained for long periods, and the extent to which it may alter lifespan remains an important unanswered question. Here we develop an experimental handle in the *C. elegans* model system, that uncovers the mechanisms that connect long-term fat oxidation with longevity. We find that sustained □-oxidation, via activation of the conserved triglyceride lipase ATGL-1, triggers a feedforward transcriptional loop that involves the mito-nuclear transcription factor ATFS-1, and a previously unknown and highly conserved repressor of ATGL-1 called HLH-11/AP4. This feedforward loop orchestrates the dual control of fat oxidation and lifespan protection, shielding the organism from life-shortening mitochondrial stress in the face of continuous fat oxidation. Thus, we uncover one mechanism by which fat oxidation can be sustained for long periods without deleterious effects on longevity.

Neuronal Control of Lipid Metabolism by STR-2 G Protein-Coupled Receptor Promotes Longevity in Caenorhabditis Elegans

The G protein-coupled receptor (GPCR) encoding family of genes constitutes more than 6% of genes in Caenorhabditis elegans genome. GPCRs control behavior, innate immunity, chemotaxis, and food search behavior. Here, we show that C. elegans longevity is regulated by a chemosensory GPCR STR-2, expressed in AWC and ASI amphid sensory neurons. STR-2 function is required at temperatures of 20°C and higher on standard Escherichia coli OP50 diet. Under these conditions, this neuronal receptor also controls health span parameters and lipid droplet (LD) homeostasis in the intestine. We show that STR-2 regulates expression of delta-9 desaturases, fat-5, fat-6 and fat-7, and of diacylglycerol acyltransferase dgat-2. Rescue of the STR-2 function in either AWC and ASI, or ASI sensory neurons alone, restores expression of fat-5, dgat-2 and restores LD stores and longevity. Rescue of stored fat levels of GPCR mutant animals to wild-type levels, with low concentration of glucose, rescues its lifespan phenotype. In all, we show that neuronal STR-2 GPCR facilitates control of neutral lipid levels and longevity in C. elegans.

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mRNA decapping is an evolutionarily conserved modulator of neuroendocrine signaling that controls development and ageing

Eukaryotic 5'–3' mRNA decay plays important roles during development and in response to stress, regulating gene expression post-transcriptionally. In *Caenorhabditis elegans*, deficiency of DCAP-1/DCP1, the essential co-factor of the major cytoplasmic mRNA decapping enzyme, impacts normal development, stress survival and ageing. Here, we show that overexpression of *dcap-1* in neurons of worms is sufficient to increase lifespan through the function of the insulin/IGF-like signaling and its effector DAF-16/FOXO transcription factor. Neuronal DCAP-1 affects basal levels of INS-7, an ageing-related insulin-like peptide, which acts in the intestine to determine lifespan. Short-lived *dcap-1* mutants exhibit a neurosecretion-dependent upregulation of intestinal *ins-7* transcription, and diminished nuclear localization of DAF-16/FOXO. Moreover, neuronal overexpression of DCP1 in *Drosophila melanogaster* confers longevity in adults, while neuronal DCP1 deficiency shortens lifespan and affects wing morphogenesis, cell non-autonomously. Our genetic analysis in two model-organisms suggests a critical and conserved function of DCAP-1/DCP1 in developmental events and lifespan modulation.

Disruption of Mitochondrial Dynamics Increases Stress Resistance Through Activation of Multiple Stress Response Pathways

Mitochondria are dynamic organelles that can change shape and size depending on the needs of the cell through the processes of mitochondrial fission and fusion. In this work, we investigated the role of mitochondrial dynamics in organismal stress response. By using C. elegans as a genetic model, we could visualize mitochondrial morphology in a live organism with well-established stress assays and well-characterized stress response pathways. We found that disrupting mitochondrial fission (DRP1/drp-1) or fusion (OPA1/eat-3, MFN/fzo-1) genes caused alterations in mitochondrial morphology that impacted both mitochondrial function and physiologic rates. While both mitochondrial fission and mitochondrial fusion mutants showed increased sensitivity to osmotic stress and anoxia, surprisingly we found that the mitochondrial fusion mutants eat-3 and fzo-1 are more resistant to both heat stress and oxidative stress. In exploring the mechanism of increased stress resistance, we found that disruption of mitochondrial fusion genes resulted in the upregulation of multiple stress response pathways. Overall, this work demonstrates that disrupting mitochondrial dynamics can have opposite effects on resistance to different types of stress. Our results suggest that disruption of mitochondrial fusion activates multiple stress response pathways that enhance resistance to specific stresses.

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Nutrient sensing pathways regulating adult reproductive diapause in *C. elegans*

Genetic and environmental manipulations, such as dietary restriction (DR), can improve both health span and lifespan in a wide range of organisms, including humans. Changes in nutrient intake trigger often overlapping metabolic pathways that can generate distinct or even opposite outputs depending on several factors, such as when DR occurs in the lifecycle of the organism or the nature of the changes in nutrients. Due to the complexity of metabolic pathways and the diversity in outputs, the underlying mechanisms regulating diet-associated pro-longevity are not yet well understood. Adult reproductive diapause (ARD) in the model organism *Caenorhabditis elegans* is a DR model that is associated with lengthened lifespan and reproductive potential (Angelo and Van Gilst 2009). As the metabolic pathways regulating ARD have not yet been explored in depth, we performed a candidate-based genetic screen analyzing select nutrient-sensing pathways to determine their contribution to the regulation of ARD. Focusing on the three phases of ARD (initiation, maintenance, and recovery), we find that ARD initiation is regulated by fatty acid metabolism, sirtuins, AMPK, and the O-linked N-acetyl glucosamine (O-GlcNAc) pathway. Although ARD maintenance was not significantly influenced by the nutrient sensors in our screen, we found that ARD recovery was modulated by energy sensing, stress response, insulin-like signaling, and the TOR pathway. We also discovered that fatty acid β-oxidation regulates ARD initiation through a pathway involving the O-GlcNAc cycling enzyme, OGT-1, acting with the nuclear hormone receptor NHR-49. Consistent with these findings, our analysis revealed a change in levels of neutral lipids associated with ARD entry defects. Our findings thus identify novel conserved genetic pathways required for ARD entry and recovery and identify new genetic interactions that provide insight into the role of OGT and OGA.

Analysis of Lifespan in C. Elegans: Low- And High-Throughput Approaches

Lifespan is the most straightforward surrogate measure of aging, as it is easily quantifiable. A common approach to measure Caenorhabditis elegans lifespan is to follow a population of animals over time and score viability based on movement. We previously developed an alternative approach, called the Replica Set method, to quantitatively measure lifespan of C. elegans in a high-throughput manner. The replica set method allows a single investigator to screen more treatments or conditions in the same amount of time without loss of data quality. The method requires common equipment found in most laboratories working with C. elegans and is thus simple to adopt. Unlike traditional approaches, the Replica Set method centers on assaying independent samples of a population at each observation point, rather than a single sample over time as with "traditional" longitudinal methods. The protocols provided here describe both the traditional experimental approach and the Replica Set method, as well as practical considerations for each.

Design and Analysis of Pharmacological Studies in Aging

Measuring lifespan of the model organism, Caenorhabditis elegans, in a 96-well format enables the screening of large chemical libraries to identify biologically active molecules. Furthermore, the wide availability of these animals with specific genetic mutations allows the identification of genes that influence lifespan, and by extension, age-related biological pathways. Here, we present a method for measuring the lifespan of C. elegans in 96-well microtiter plates to identify and study pharmacologically active molecules that extend lifespan. The format of this assay is readily adapted for automated liquid handling systems and imaging of phenotypes.

Measurements of Innate Immune Function in C. Elegans

The microscopic nematode Caenorhabditis elegans has emerged as a powerful system to characterize evolutionarily ancient mechanisms of pathogen sensing, innate immune activation, and protective host responses. Experimentally, C. elegans can be infected with a wide variety of human pathogens, as well as with natural pathogens of worms that were isolated from wild-caught nematodes. Here, we focus on an experimental model of bacterial pathogenesis that utilizes the human opportunistic bacterial pathogen Pseudomonas aeruginosa and present an algorithm that can be used to study mechanisms of immune function in nematodes. An initial comparison of the susceptibility of a C. elegans mutant to P. aeruginosa infection with its normal lifespan permits an understanding of a mutant's effect on pathogen susceptibility in the context of potential pleotropic consequences on general worm fitness. Assessing the behavior of nematodes in the presence of P. aeruginosa can also help determine if a gene of interest modulates pathogen susceptibility by affecting the host's ability to avoid a pathogen. In addition, quantification of the pathogen load in the C. elegans intestine during infection, characterization of immune effector transcription that are regulated by host defense pathways and an initial assessment of tissue specificity of immune gene function can refine hypotheses about the mechanism of action of a gene of interest. Together, these protocols offer one approach to characterize novel host defense mechanisms in a simple metazoan host.

Transcriptional Profiling of C. Elegans Adult Cells and Tissues With Age

Multicellular organisms are composed of distinct cells and tissues that coordinate highly orchestrated responses to environmental challenges, including those that arise with age. Since C. elegans is a premier model system used to study the molecular and cellular regulators of adult and aging phenotypes, cell type- and tissue-specific approaches are needed to characterize the genome-wide expression changes associated with these responses. Here we describe a method for the FACS-based isolation and RNA sequencing of dissociated cells from adult C. elegans. This technique is amenable to profiling the cell- and tissue-specific gene expression changes in C. elegans mutants, including aging models, such as the daf-2/insulin-like signaling (IIS) pathway, and in wild-type animals with age.

Asessing Tissue-Specific Autophagy Flux in Adult Caenorhabditis Elegans

The cellular recycling process of autophagy is essential for survival, development, and homeostasis. Autophagy also plays an important role in aging and has been linked to longevity in many species, including the nematode C. elegans. Study of the physiological roles of autophagy during C. elegans aging requires methods for the spatiotemporal analysis of autophagy. Here we describe a method for assessing autophagic flux in multiple tissues of C. elegans by quantifying the pool of autophagic vesicles using fluorescently labelled Atg8/LGG-1 reporters upon autophagy inhibition using bafilomycin A_1 (BafA). This methodology has revealed that autophagic activity varies in different cell types of C. elegans during aging.

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Serotonin signaling by maternal neurons upon stress ensures progeny survival

Germ cells are vulnerable to stress. Therefore, how organisms protect their future progeny from damage in a fluctuating environment is a fundamental question in biology. We show that in *Caenorhabditis elegans*, serotonin released by maternal neurons during stress ensures the viability and stress resilience of future offspring. Serotonin acts through a signal transduction pathway conserved between *C. elegans* and mammalian cells to enable the transcription factor HSF1 to alter chromatin in soon-to-be fertilized germ cells by recruiting the histone chaperone FACT, displacing histones, and initiating protective gene expression. Without serotonin release by maternal neurons, FACT is not recruited by HSF1 in germ cells, transcription occurs but is delayed, and progeny of stressed *C. elegans* mothers fail to complete development. These studies uncover a novel mechanism by which stress sensing by neurons is coupled to transcription response times of germ cells to protect future offspring.

REVIEWS/COMMENTS/ METHODS/EDITORIALS

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The quest to slow ageing through drug discovery

Linda Partridge, Matias Fuentealba & Brian K. Kennedy

Although death is inevitable, individuals have long sought to alter the course of the ageing process. Indeed, ageing has proved to be modifiable; by intervening in biological systems, such as nutrient sensing, cellular senescence, the systemic environment and the gut microbiome, phenotypes of ageing can be slowed sufficiently to mitigate age-related functional decline. These interventions can also delay the onset of many disabling, chronic diseases, including cancer, cardiovascular disease and neurodegeneration, in animal models. Here, we examine the most promising interventions to slow ageing and group them into two tiers based on the robustness of the preclinical, and some clinical, results, in which the top tier includes rapamycin, senolytics, metformin, acarbose, spermidine, NAD^+ enhancers and lithium. We then focus on the potential of the interventions and the feasibility of conducting clinical trials with these agents, with the overall aim of maintaining health for longer before the end of life.

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Effect of low-dose aspirin on health outcomes: An umbrella review of systematic reviews and meta-analyses

Methods

Aspirin is associated with several health outcomes, but the overall benefit/risk balance related to aspirin use is unclear. We searched three major databases up to 15 August 2019 for meta-analyses of observational studies and randomized controlled trials (RCTs) including low-dose aspirin compared to placebo or other treatments. Based on random-effects summary effect sizes, 95% prediction intervals, heterogeneity, small-study effects and excess significance, significant meta-analyses of observational studies were classified from convincing (class I) to weak (class IV). For meta-analyses of RCTs, outcomes with random effects *P* -value < .005 and a moderate/high GRADE assessment, were classified as strong evidence. From 6802 hits, 67 meta-analyses (156 outcomes) were eligible.

Results

Observational data showed highly suggestive evidence for aspirin use and increased risk of upper gastrointestinal bleeding (RR = 2.28, 95% CI: 1.97–2.64). In RCTs of low-dose aspirin, we observed strong evidence for lower risk of CVD in people without CVD (RR = 0.83; 95% CI: 0.79–0.87) and in general population (RR = 0.83; 95% CI: 0.79–0.89), higher risk of major gastrointestinal (RR = 1.47; 95% CI: 1.26–1.72) and intracranial bleeding (RR = 1.34; 95% CI: 1.18–1.53), and of major bleedings in people without CVD (RR = 1.62; 95% CI: 1.26–2.08).

Conclusion

Compared to other active medications, low-dose aspirin had strong evidence for lower risk of bleeding, but also lower comparative efficacy. Low-dose aspirin significantly lowers CVD risk and increases risk of bleeding. Evidence for multiple other health outcomes is limited.

The Human Body as a Super Network: Digital Methods to Analyze the Propagation of Aging

Biological aging is a complex process involving multiple biological processes. These can be understood theoretically though considering them as individual networks—e.g., epigenetic networks, cell-cell networks (such as astroglial networks), and population genetics. Mathematical modeling allows the combination of such networks so that they may be studied in unison, to better understand how the so-called "seven pillars of aging" combine and to generate hypothesis for treating aging as a condition at relatively early biological ages. In this review, we consider how recent progression in mathematical modeling can be utilized to investigate aging, particularly in, but not exclusive to, the context of degenerative neuronal disease. We also consider how the latest techniques for generating biomarker models for disease prediction, such as longitudinal analysis and parenclitic analysis can be applied to as both biomarker platforms for aging, as well as to better understand the inescapable condition. This review is written by a highly diverse and multi-disciplinary team of scientists from across the globe and calls for greater collaboration between diverse fields of research.

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Normal ageing of the brain: Histological and biological aspects

All the hallmarks of ageing are observed in the brain, and its cells, especially neurons, are characterized by their remarkably long lifetime. Like any organ or system, the brain is exposed to ageing processes which affect molecules, cells, blood vessels, gross morphology and, uniquely for this organ, cognition. The preponderant cerebral structures are characterized by the cellular processes of neurons and glial cells and while the quantity of cerebral interstitial fluid is limited, it is now recognized as playing a crucial role in maintaining cerebral homeostasis. Most of our current knowledge of the ageing brain derives from studies of neurodegenerative disorders. It is interesting to note that common features of these disorders, like Tau, phosphoTau and amyloid peptide accumulation, can begin relatively early in life as a result of physiological ageing and are present in subclinical cases while also being used as early-stage markers of neurodegenerative diseases in progression. In this article, we review tissue and cellular modifications in the ageing brain. Commonly described macroscopic, microscopic and vascular changes that in the ageing brain are contrasted with those seen in neurodegenerative contexts. We also review the molecular changes that occur with age in the brain, such as modifications in gene expression, insulin/insulin-like growth factor 1 signalling dysfunction, post-translational protein modifications, mitochondrial dysfunction, autophagy and calcium conductance changes.

Redox Modifications in Synaptic Components as Biomarkers of Cognitive Status, in Brain Aging and Disease

Aging is a natural process that includes several changes that gradually make organisms degenerate and die. Harman's theory proposes that aging is a consequence of the progressive accumulation of oxidative modifications mediated by reactive oxygen/nitrogen species, which plays an essential role in the development and progression of many neurodegenerative diseases. This review will focus on how abnormal redox modifications induced by age impair the functionality of neuronal redox-sensitive proteins involved in axonal elongation and guidance, synaptic plasticity, and intercellular communication. We will discuss post-transcriptional regulation of gene expression by microRNAs as a mechanism that controls the neuronal redox state. Finally, we will discuss how some brain-permeant antioxidants from the diet have a beneficial effect on cognition. Taken together, the evidence revised here indicates that oxidative-driven modifications of specific proteins and changes in microRNA expression may be useful biomarkers for aging and neurodegenerative diseases. Also, some specific antioxidant therapies have undoubtedly beneficial neuroprotective effects when administered in the correct doses, in the ideal formulation combination, and during the appropriate therapeutic window. The use of some antioxidants is, therefore, still poorly explored for the treatment of neurodegenerative diseases such as Alzheimer's disease.

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The Power of Proteomics to Monitor Senescence–Associated Secretory Phenotypes and Beyond: Toward Clinical Applications

Introduction: Cellular senescence is a rapidly growing field with potential relevance for the treatment of multiple human diseases. In the last decade, cellular senescence and the senescence-associated secretory phenotype (SASP) have emerged as central drivers of aging and many chronic diseases, including cancer, neurodegeneration, heart disease and osteoarthritis. Major efforts are underway to develop drugs that selectively eliminate senescent cells (senolytics) or alter the SASP (senomorphics) to treat age-related diseases in humans. The translation of senescence-targeting therapies into humans is still in early stages. Nonetheless, it is clear that proteomic approaches will facilitate the discovery of important SASP proteins, development of senescence- and SASP-derived biomarkers, and identification of therapeutic targets for senolytic and senomorphic drugs.**Areas covered**: We review recent proteomic studies of cellular senescence and their translational relevance and, particularly, characterization of the secretory phenotype and preclinical development of biomarkers (from 2008-2020, PubMed). We focus on emerging areas, such as the heterogeneity of senescent cells and the SASP, extracellular vesicles released by senescent cells, and validating biomarkers of aging in vivo.**Expert opinion**: Proteomic and multi-omic approaches will be important for the development of senescence-based biomarkers to facilitate and monitor future therapeutic interventions that target senescent cells.

Folding the Mitochondrial UPR Into the Integrated Stress Response

Eukaryotic cells must accurately monitor the integrity of the mitochondrial network to overcome environmental insults and respond to physiological cues. The mitochondrial unfolded protein response (UPR^{mt}) is a mitochondrial-to-nuclear signaling pathway that maintains mitochondrial proteostasis, mediates signaling between tissues, and regulates organismal aging. Aberrant UPR^{mt} signaling is associated with a wide spectrum of disorders, including congenital diseases as well as cancers and neurodegenerative diseases. Here, we review recent research into the mechanisms underlying UPR^{mt} signaling in Caenorhabditis elegans and discuss emerging connections between the UPR^{mt} signaling and a translational regulation program called the 'integrated stress response'. Further study of the UPR^{mt} will potentially enable development of new therapeutic strategies for inherited metabolic disorders and diseases of aging.

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Dysfunction and toxicity of damaged proteins in the etiology of aging and age-related degenerative and malignant diseases

Health can be defined as a harmony, or homeostasis, of the activities of thousands of different proteins, whereas aging and diseases result from their disharmony manifested at the levels of cells and tissues. Such disharmony is caused primarily by dysfunction and toxicity of misfolded proteins damaged by oxidation. This is an overview of key data that inspired new concepts allowing interpretation and integration of the scientific literature on aging and age-related diseases. These concepts suggest strategies for prevention and attenuation of age-related degenerative and malignant diseases mimicking the life of super-centenarians.

A Molecular Perspective on Age-Dependent Changes to the Heat Shock Axis

Aging is a complex process associated with progressive damage that leads to cellular dysfunction often accompanied by frailty and age-related diseases. Coping with all types of physiologic stress declines with age. While representing a primordial, cross-species response in poikilo- and homeotherms, the age-dependent perturbation of the stress response is more complex than previously thought. This short review examines how age influences the stress axis at multiple levels that involve both activating and attenuating pathways.

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Mitochondrial cross-compartmental signalling to maintain proteostasis and longevity

Lifespan in eukaryotic species can be prolonged by shifting from cellular states favouring growth to those favouring maintenance and stress resistance. For instance, perturbations in mitochondrial oxidative phosphorylation (OXPHOS) can shift cells into this latter state and extend lifespan. Because mitochondria rely on proteins synthesized from nuclear as well as mitochondrial DNA, they need to constantly send and receive messages from other compartments of the cell in order to function properly and maintain homeostasis, and lifespan extension is often dependent on this cross-compartmental signalling. Here, we describe the mechanisms of bi-directional mitochondrial cross-compartmental signalling resulting in proteostasis and longevity. These proteostasis mechanisms are highly context-dependent, governed by the origin and extent of stress. Furthermore, we discuss the translatability of these mechanisms and explore therapeutic developments, such as the antibiotic studies targeting mitochondria or mitochondria-derived peptides as therapies for age-related diseases such as neurodegeneration and cancer.

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Mechanisms of Lifespan Regulation by Calorie Restriction and Intermittent Fasting in Model Organisms

Genetic and pharmacological interventions have successfully extended healthspan and lifespan in animals, but their genetic interventions are not appropriate options for human applications and pharmacological intervention needs more solid clinical evidence. Consequently, dietary manipulations are the only practical and probable strategies to promote health and longevity in humans. Caloric restriction (CR), reduction of calorie intake to a level that does not compromise overall health, has been considered as being one of the most promising dietary interventions to extend lifespan in humans. Although it is straightforward, continuous reduction of calorie or food intake is not easy to practice in real lives of humans. Recently, fasting-related interventions such as intermittent fasting (IF) and time-restricted feeding (TRF) have emerged as alternatives of CR. Here, we review the history of CR and fasting-related strategies in animal models, discuss the molecular mechanisms underlying these interventions, and propose future directions that can fill the missing gaps in the current understanding of these dietary interventions. CR and fasting appear to extend lifespan by both partially overlapping common mechanisms such as the target of rapamycin (TOR) pathway and circadian clock, and distinct independent mechanisms that remain to be discovered. We propose that a systems approach combining global transcriptomic, metabolomic, and proteomic analyses followed by genetic perturbation studies targeting multiple candidate pathways will allow us to better understand how CR and fasting interact with each other to promote longevity.

Ageing and Longevity Genes in Cardiovascular Diseases

Over the last century, Western societies experienced a demographic shift driven by increased lifespan and decreased fertility, resulting in the subversion of the world's demographic pyramid. In ageing societies, cardiovascular diseases are the major cause of morbidity and mortality, thus representing a major societal and economic burden. Indeed, ageing associates with the deterioration of a genetic network implicated in senescence and longevity, orchestrating deleterious cellular processes that converge in the structural and functional decline of both the myocardium and the vasculature. In this review, we revise a compendium of genes involved in these processes and delineate possible strategies to interfere with them. Dietary interventions (e.g. intermittent fasting) and sirtuin-activating compounds are among the most promising interventions shown to promote protective effects on the ageing cardiovascular system. We conclude that ageing and longevity genes modulate cardiovascular function by acting on deleterious downstream processes such as inflammation and oxidative stress, thus representing promising targets for the prevention and treatment of age-related cardiovascular dysfunction.

Role of immune cells in the removal of deleterious senescent cells

Cellular senescence is an essentially irreversible arrest of cell proliferation coupled to a complex senescence-associated secretory phenotype (SASP). The senescence arrest prevents the development of cancer, and the SASP can promote tissue repair. Recent data suggest that the prolonged presence of senescent cells, and especially the SASP, could be deleterious, and their beneficial effects early in life can become maladaptive such that they drive aging phenotypes and pathologies late in life. It is therefore important to develop strategies to eliminate senescent cells. There are currently under development or approved several immune cell-based therapies for cancer, which could be redesigned to target senescent cells. This review focuses on this possible use of immune cells and discusses how current cell-based therapies could be used for senescent cell removal.

OTHER RESEARCH & REVIEWS

Generation and Profiling of 2,135 Human ESC Lines for the Systematic Analyses of Cell States Perturbed by Inducing Single Transcription Factors

Transcription factors (TFs) play a pivotal role in determining cell states, yet our understanding of the causative relationship between TFs and cell states is limited. Here, we systematically examine the state changes of human pluripotent embryonic stem cells (hESCs) by the large-scale manipulation of single TFs. We establish 2,135 hESC lines, representing three clones each of 714 doxycycline (Dox)-inducible genes including 481 TFs, and obtain 26,998 microscopic cell images and 2,174 transcriptome datasets-RNA sequencing (RNA-seq) or microarrays-48 h after the presence or absence of Dox. Interestingly, the expression of essentially all the genes, including genes located in heterochromatin regions, are perturbed by these TFs. TFs are also characterized by their ability to induce differentiation of hESCs into specific cell lineages. These analyses help to provide a way of classifying TFs and identifying specific sets of TFs for directing hESC differentiation into desired cell types.

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A Dual-Mechanism Antibiotic Kills Gram-Negative Bacteria and Avoids Drug Resistance

The rise of antibiotic resistance and declining discovery of new antibiotics has created a global health crisis. Of particular concern, no new antibiotic classes have been approved for treating Gram-negative pathogens in decades. Here, we characterize a compound, SCH-79797, that kills both Gram-negative and Gram-positive bacteria through a unique dual-targeting mechanism of action (MoA) with undetectably low resistance frequencies. To characterize its MoA, we combined quantitative imaging, proteomic, genetic, metabolomic, and cell-based assays. This pipeline demonstrates that SCH-79797 has two independent cellular targets, folate metabolism and bacterial membrane integrity, and outperforms combination treatments in killing methicillin-resistant *Staphylococcus aureus* (MRSA) persisters. Building on the molecular core of SCH-79797, we developed a derivative, Irresistin-16, with increased potency and showed its efficacy against *Neisseria gonorrhoeae* in a mouse vaginal infection model. This promising antibiotic lead suggests that combining multiple MoAs onto a single chemical scaffold may be an underappreciated approach to targeting challenging bacterial pathogens.

An Azidoribose Probe to Track Ketoamine Adducts in Histone Ribose Glycation

Igor Maksimovic, Qingfei Zheng, Marissa N. Trujillo, James J. Galligan, and Yael David*

Reactive cellular metabolites can modify macromolecules and form adducts known as nonenzymatic covalent modifications (NECMs). The dissection of the mechanisms, regulation, and consequences of NECMs, such as glycation, has been challenging due to the complex and often ambiguous nature of the adducts formed. Specific chemical tools are required to directly track the formation of these modifications on key targets in order to uncover their underlying physiological importance. Here, we present the novel chemoenzymatic synthesis of an active azido-modified ribose analog, 5-azidoribose (**5-AR**), as well as the synthesis of an inactive control derivative, 1-azidoribose (**1-AR**), and their application toward understanding protein ribose-glycation *in vitro* and *in cellulo*. With these new probes we found that, similar to methylglyoxal (MGO) glycation, ribose glycation specifically accumulates on histones. In addition to fluorescent labeling, we demonstrate the utility of the probe in enriching modified targets, which were identified by label-free quantitative proteomics and high-resolution MS/MS workflows. Finally, we establish that the known oncoprotein and hexose deglycase, fructosamine 3-kinase (FN3K), recognizes and facilitates the removal of **5-AR** glycation adducts in live cells, supporting the dynamic regulation of ribose glycation as well as validating the probe as a new platform to monitor FN3K activity. Altogether, we demonstrate this probe's utilities to uncover ribose-glycation and deglycation events as well as track FN3K activity toward establishing its potential as a new cancer vulnerability.