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Scientific News
5th of July 2020
Sven Bulterijs

Business/Conferences/ General news

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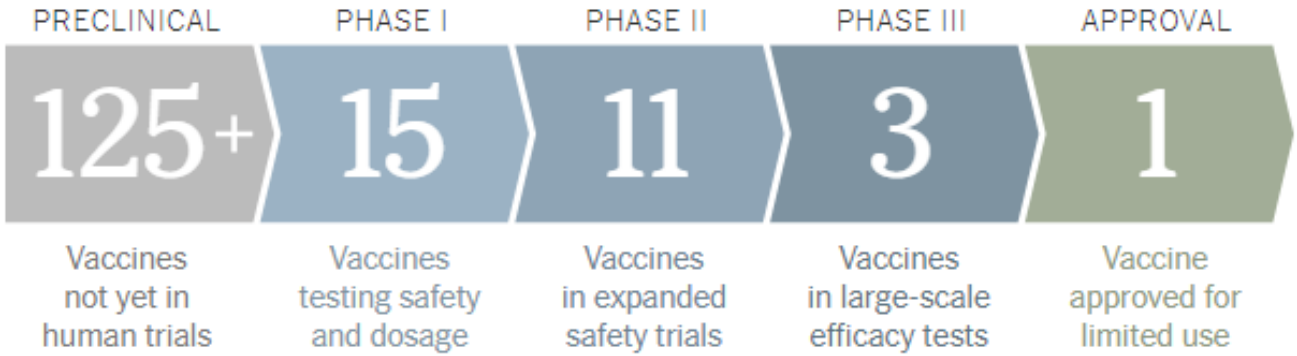
The New York Times

Coronavirus Vaccine Tracker

By Jonathan Corum, Denise Grady, Sui-Lee Wee and Carl Zimmer Updated July 3, 2020



Researchers around the world are developing more than 145 vaccines against the coronavirus, and 21 vaccines are in human trials. Vaccines typically require years of research and testing before reaching the clinic, but scientists are racing to produce a safe and effective vaccine by next year.

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Coronavirus vaccine developers wary of errant antibodies

Concerns persist that COVID-19 vaccines could cause antibody-dependent enhancement, which can potentiate viral entry into host cells and worsen disease.

Knack Rubrieken ▾ Het magazine Voordelen voor abonnees Abonneren

Indien er een coronavaccin ter beschikking komt, zal u zich dan laten vaccineren?

Ja

22%

Nee

73%

Ik weet het nog niet

5%

reeds 14586 stemmen

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Even covid-19 can't kill the anti-vaccination movement

BMJ 2020 ; 369 doi: https://doi.org/10.1136/bmj.m2184 (Published 04 June 2020)
Cite this as: *BMJ* 2020;369:m2184

During a pandemic, you might expect everyone to say they want a vaccine—but that's not what a study of 1000 people in New York over 24-26 April found.

"Only 59% of respondents said they would get a vaccine and only 53% would give it to their children," says Scott Ratzan, distinguished lecturer at the New York based CUNY Graduate School of Public Health and Health Policy.[1]

Since the project began in March, Ratzen's group has asked the question three times, and each time the proportion is low. "It's concerning. I would have thought numbers would go up. I didn't expect to see it so negative."

In their first poll on 27-29 March, 62% said they would have a coronavirus vaccine, with 19% saying they would decline it and 19% unsure. The latest poll, conducted at the start of May, found that 31% would have a vaccine immediately with 48% saying they would if their doctor recommended it; 12% would reject a vaccine outright. Ratzan also asked if they would volunteer for a coronavirus vaccine clinical trial. Just 31% expressed an interest.

He attributes much of the negativity in his surveys around a coronavirus vaccine to a small but incredibly vocal movement. "The anti-vaccination movement is going to make covid-19 more difficult to get under control," he told *The BMJ*.

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Targets of T Cell Responses to SARS-CoV-2 Coronavirus in Humans with COVID-19 Disease and Unexposed Individuals

Understanding adaptive immunity to SARS-CoV-2 is important for vaccine development, interpreting coronavirus disease 2019 (COVID-19) pathogenesis, and calibration of pandemic control measures. Using HLA class I and II predicted peptide "megapools," circulating SARS-CoV-2-specific $CD8^+$ and $CD4^+$ T cells were identified in ~70% and 100% of COVID-19 convalescent patients, respectively. $CD4^+$ T cell responses to spike, the main target of most **vaccine efforts, were robust and correlated with** the magnitude of the anti-SARS-CoV-2 IgG and IgA titers. The M, spike, and N proteins each accounted for 11%–27% of the total $CD4^+$ response, with additional responses commonly targeting nsp3, nsp4, ORF3a, and ORF8, among others. For $CD8^+$ T cells, spike and M were recognized, with at least eight SARS-CoV-2 ORFs targeted. Importantly, we detected SARS-CoV-2-reactive $CD4^+$ T cells in ~40%–60% of unexposed individuals, suggesting cross-reactive T cell recognition between circulating "common cold" coronaviruses and SARS-CoV-2.

Primary exposure to SARS-CoV-2 protects against reinfection in rhesus macaques

Coronavirus disease 2019 (COVID-19), which is caused by infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become a global pandemic. It currently remains unclear whether convalescing patients have a risk of reinfection. We generated a rhesus macaque model of SARS-CoV-2 infection that was characterized by interstitial pneumonia and systemic viral dissemination mainly in the respiratory and gastrointestinal tracts. Rhesus macaques reinfected with the identical SARS-CoV-2 strain during the early recovery phase of the initial SARS-CoV-2 infection did not show detectable viral dissemination, clinical manifestations of viral disease, or histopathological changes. Comparing the humoral and cellular immunity between primary infection and rechallenge revealed notably enhanced neutralizing antibody and immune responses. Our results suggest that primary SARS-CoV-2 exposure protects against subsequent reinfection in rhesus macaques.

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Robust T cell immunity in convalescent individuals with asymptomatic or mild COVID-19

SARS-CoV-2-specific memory T cells will likely prove critical for long-term immune protection against COVID-19. We systematically mapped the functional and phenotypic landscape of SARS-CoV-2-specific T cell responses in a large cohort of unexposed individuals as well as exposed family members and individuals with acute or convalescent COVID-19. Acute phase SARS-CoV-2-specific T cells displayed a highly activated cytotoxic phenotype that correlated with various clinical markers of disease severity, whereas convalescent phase SARS-CoV-2-specific T cells were polyfunctional and displayed a stem-like memory phenotype. Importantly, SARS-CoV-2-specific T cells were detectable in antibody-seronegative family members and individuals with a history of asymptomatic or mild COVID-19. Our collective dataset shows that SARS-CoV-2 elicits robust memory T cell responses akin to those observed in the context of successful vaccines, suggesting that natural exposure or infection may prevent recurrent episodes of severe COVID-19 also in seronegative individuals.

Reducing transmission of SARS-CoV-2

Kimberly A. Prather[1], Chia C. Wang[2,3], Robert T. Schooley[4]
+ See all authors and affiliations

Respiratory infections occur through the transmission of virus-containing droplets (>5 to 10 μm) and aerosols (≤5 μm) exhaled from infected individuals during breathing, speaking, coughing, and sneezing. Traditional respiratory disease control measures are designed to reduce transmission by droplets produced in the sneezes and coughs of infected individuals. However, a large proportion of the spread of coronavirus disease 2019 (COVID-19) appears to be occurring through airborne transmission of aerosols produced by asymptomatic individuals during breathing and speaking (*1*—*3*). Aerosols can accumulate, remain infectious in indoor air for hours, and be easily inhaled deep into the lungs. For society to resume, measures designed to reduce aerosol transmission must be implemented, including universal masking and regular, widespread testing to identify and isolate infected asymptomatic individuals.

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A modelling framework to assess the likely effectiveness of facemasks in combination with 'lock-down' in managing the COVID-19 pandemic

COVID-19 is characterized by an infectious pre-symptomatic period, when newly infected individuals can unwittingly infect others. We are interested in what benefits facemasks could offer as a non-pharmaceutical intervention, especially in the settings where high-technology interventions, such as contact tracing using mobile apps or rapid case detection via molecular tests, are not sustainable. Here, we report the results of two mathematical models and show that facemask use by the public could make a major contribution to reducing the impact of the COVID-19 pandemic. Our intention is to provide a simple modelling framework to examine the dynamics of COVID-19 epidemics when facemasks are worn by the public, with or without imposed 'lock-down' periods. Our results are illustrated for a number of plausible values for parameter ranges describing epidemiological processes and mechanistic properties of facemasks, in the absence of current measurements for these values. We show that, when facemasks are used by the public all the time (not just from when symptoms first appear), the effective reproduction number, R_e, can be decreased below 1, leading to the mitigation of epidemic spread. Under certain conditions, when lock-down periods are implemented in combination with 100% facemask use, there is vastly less disease spread, secondary and tertiary waves are flattened and the epidemic is brought under control. The effect occurs even when it is assumed that facemasks are only 50% effective at capturing exhaled virus inoculum with an equal or lower efficiency on inhalation. Facemask use by the public has been suggested to be ineffective because wearers may touch their faces more often, thus increasing the probability of contracting COVID-19. For completeness, our models show that facemask adoption provides population-level benefits, even in circumstances where wearers are placed at increased risk. At the time of writing, facemask use by the public has not been recommended in many countries, but a recommendation for wearing face-coverings has just been announced for Scotland. Even if facemask use began after the start of the first lock-down period, our results show that benefits could still accrue by reducing the risk of the occurrence of further COVID-19 waves. We examine the effects of different rates of facemask adoption without lock-down periods and show that, even at lower levels of adoption, benefits accrue to the facemask wearers. These analyses may explain why some countries, where adoption of facemask use by the public is around 100%, have experienced significantly lower rates of COVID-19 spread and associated deaths. We conclude that facemask use by the public, when used in combination with physical distancing or periods of lock-down, may provide an acceptable way of managing the COVID-19 pandemic and re-opening economic activity. These results are relevant to the developed as well as the developing world, where large numbers of people are resource poor, but fabrication of home-made, effective facemasks is possible. A key message from our analyses to aid the widespread adoption of facemasks would be: 'my mask protects you, your mask protects me'.


vtmnieuws
GROTE STUDIE: 77% WIL MONDMASKER VERPLICHTEN IN SUPERMARKT

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Column: How a retracted research paper coronavirus research

The Lancet, one of the most prestigious journals in the world, gave this paper its scarlet letter. (The Lancet)

By MICHAEL HILTZIK | BUSINESS COLUMNIST

JUNE 8, 2020 | 2:53 PM

Call it the retraction that shook the coronavirus world.

On June 4, the Lancet, the British medical journal that is one of the most prestigious scientific publications in the world, withdrew a paper that had been one of the most consequential in the novel field of coronavirus studies.

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It's the end of road for hydroxychloroquine in COVID-19 as Novartis, NIH and WHO pull out of trials

by Angus Liu | Jun 22, 2020 10:05am

The road for hydroxychloroquine against COVID-19 is coming to an end. Three major clinical programs have been terminated after a U.K. trial found "no clinical benefit" for the malaria drug championed by U.S. President Donald Trump.

In the past few days, the World Health Organization (WHO), generic hydroxychloroquine (HCQ) maker Novartis and the U.S. National Institutes of Health (NIH) have all ended their HCQ COVID-19 studies in hospitalized patients in quick succession.

The WHO and NIH cited lack of benefits for patients, while Novartis blamed "acute enrollment challenges."

Numerous investigator-sponsored trials may still be underway, but none of them has the scale of these three to yield any convincing results. Sanofi previously put a temporary halt to its own study based on safety concerns but has not since resumed recruitment, meaning the latest three terminations were likely the final judgement for HCQ's use in COVID-19.

China first included HCQ in its COVID-19 treatment guidelines, but it was Trump who promoted the med to global attention after labeling it a "game changer." Clinical trials were launched to prove its efficacy, and the FDA quickly doled out an emergency use authorization.

But several relatively small clinical trials, including an early one from China and a U.S. Department of Veterans Affairs study, have failed to find the drug's worth. Its potential risk for serious side effects didn't build confidence, either.

A controversial study in The Lancet previously led to a temporary halt of the HCQ arm in the WHO Solidarity trial, though it was soon resumed once the paper was found to be based on a dubious source of registry data and therefore was retracted by the authors.

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Treatment with Hydroxychloroquine, Azithromycin, and Combination in Patients Hospitalized with COVID-19

Results

Of 2,541 patients, with a median total hospitalization time of 6 days (IQR: 4-10 days), median age was 64 years (IQR:53-76 years), 51% male, 56% African American, with median time to follow-up of 28.5 days (IQR:3-53). Overall in-hospital mortality was 18.1% (95% CI:16.6%-19.7%); by treatment: hydroxychloroquine + azithromycin, 157/783 (20.1% [95% CI: 17.3%-23.0%]), hydroxychloroquine alone, 162/1202 (13.5% [95% CI: 11.6%-15.5%]), azithromycin alone, 33/147 (22.4% [95% CI: 16.0%-30.1%]), and neither drug, 108/409 (26.4% [95% CI: 22.2%-31.0%]). Primary cause of mortality was respiratory failure (88%); no patient had documented torsades de pointes. From Cox regression modeling, predictors of mortality were age≥65 years (HR:2.6 [95% CI:1.9-3.3]), white race (HR:1.7 [95% CI:1.4-2.1]), CKD (HR:1.7 [95%CI:1.4-2.1]), reduced O2 saturation level on admission (HR:1.5 [95%CI:1.1-2.1]), and ventilator use during admission (HR: 2.2 [95%CI:1.4-3.3]). Hydroxychloroquine provided a 66% hazard ratio reduction, and hydroxychloroquine + azithromycin 71% compared to neither treatment ($p < 0.001$).

Conclusions and Relevance

In this multi-hospital assessment, when controlling for COVID-19 risk factors, treatment with hydroxychloroquine alone and in combination with azithromycin was associated with reduction in COVID-19 associated mortality. Prospective trials are needed to examine this impact.

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Risk Factors for 2019 Novel Coronavirus Disease (COVID-19) Patients Progressing to Critical Illness: A Systematic Review and Meta-Analysis

Importance: With the rising number of COVID-19 cases, global health resources are strained by the pandemic. No proven effective therapies or vaccines for this virus are currently available. In order to maximize the use of limited medical resources, distinguishing between mild and severe patients as early as possible has become pivotal.

Objective: To systematically review evidence for the risk factors of COVID-19 patients progressing to critical illness.

Evidence review: We conducted a comprehensive search for primary literature in both Chinese and English electronic bibliographic databases. The American agency for health research and quality tool was used for quality assessment. A meta-analysis was undertaken using STATA version 15.0.

Results: Twenty articles (4062 patients) were eligible for this systematic review and meta-analysis. First and foremost, we observed that elderly male patients with a high body mass index, high breathing rate and a combination of underlying diseases (such as hypertension, diabetes, cardiovascular disease, and chronic obstructive pulmonary disease) were more likely to develop severe COVID-19 infections. Second, compared with non-severe patients, severe patients had more serious symptoms such as fever and dyspnea. Besides, abnormal laboratory tests were more prevalent in severe patients than in mild cases, such as elevated levels of white blood cell counts, liver enzymes, lactate dehydrogenase, creatine kinase, C-reactive protein and procalcitonin, as well as decreased levels of lymphocytes and albumin.

Interpretation: This is the first systematic review exploring the risk factors for severe illness in COVID-19 patients. Our study may be helpful for clinical decision-making and optimizing resource allocation.

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Decreased Naïve T-cell Production Leading to Cytokine Storm as Cause of Increased COVID-19 Severity with Comorbidities

Aging, type 2 diabetes, and male gender are major risk factors leading to increased COVID-19 morbidity and mortality. Thymic production and the export of naïve T cells decrease with aging through the effects of androgens in males and in type 2 diabetes. Furthermore, with aging, recovery of naïve T-cell populations after bone marrow transplantation is delayed and associated with an increased risk of chronic graft vs. host disease. Severe COVID-19 and SARS infections are notable for severe T-cell depletion. In COVID-19, there is unique suppression of interferon signaling by infected respiratory tract cells with intact cytokine signaling. A decreased naïve T-cell response likely contributes to an excessive inflammatory response and increases the odds of a cytokine storm. Treatments that improve naïve T-cell production may prove to be vital COVID-19 therapies, especially for these high-risk groups.

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Diagnostic accuracy of serological tests for covid-19: systematic review and meta-analysis

Eligibility criteria and data analysis Eligible studies measured sensitivity or specificity, or both of a covid-19 serological test compared with a reference standard of viral culture or reverse transcriptase polymerase chain reaction. Studies were excluded with fewer than five participants or samples. Risk of bias was assessed using quality assessment of diagnostic accuracy studies 2 (QUADAS-2). Pooled sensitivity and specificity were estimated using random effects bivariate meta-analyses.

Main outcome measures The primary outcome was overall sensitivity and specificity, stratified by method of serological testing (enzyme linked immunosorbent assays (ELISAs), lateral flow immunoassays (LFIAs), or chemiluminescent immunoassays (CLIAs)) and immunoglobulin class (IgG, IgM, or both). Secondary outcomes were stratum specific sensitivity and specificity within subgroups defined by study or participant characteristics, including time since symptom onset.

Results 5016 references were identified and 40 studies included. 49 risk of bias assessments were carried out (one for each population and method evaluated). High risk of patient selection bias was found in 98% (48/49) of assessments and high or unclear risk of bias from performance or interpretation of the serological test in 73% (36/49). Only 10% (4/40) of studies included outpatients. Only two studies evaluated tests at the point of care. For each method of testing, pooled sensitivity and specificity were not associated with the immunoglobulin class measured. The pooled sensitivity of ELISAs measuring IgG or IgM was 84.3% (95% confidence interval 75.6% to 90.9%), of LFIAs was 66.0% (49.3% to 79.3%), and of CLIAs was 97.8% (46.2% to 100%). In all analyses, pooled sensitivity was lower for LFIAs, the potential point-of-care method. Pooled specificities ranged from 96.6% to 99.7%. Of the samples used for estimating specificity, 83% (10 465/12 547) were from populations tested before the epidemic or not suspected of having covid-19. Among LFIAs, pooled sensitivity of commercial kits (65.0%, 49.0% to 78.2%) was lower than that of non-commercial tests (88.2%, 83.6% to 91.3%). Heterogeneity was seen in all analyses. Sensitivity was higher at least three weeks after symptom onset (ranging from 69.9% to 98.9%) compared with within the first week (from 13.4% to 50.3%).

Conclusion Higher quality clinical studies assessing the diagnostic accuracy of serological tests for covid-19 are urgently needed. Currently, available evidence does not support the continued use of existing point-of-care serological tests.

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After patients die, FDA clamps hold on Astellas gene therapy trial

by Nick Paul Taylor | Jun 29, 2020 8:20am

A second patient has died after receiving Audentes Therapeutics' gene therapy against a rare genetic neuromuscular disorder. Audentes, which Astellas Pharma acquired for $3 billion, has dropped plans to file for approval imminently and paused a clinical trial while it reviews the situation.

In May, Audentes told patient groups that a person with X-linked myotubular myopathy (XLMTM) had died after receiving AT132, a gene therapy that uses an AAV8 vector to deliver a working copy of the myotubularin 1 gene. The patient, one of three older individuals to receive the higher dose of AT132, died from sepsis.

Now, Audentes has shared details of a second death. The patient was another one of the three older individuals to receive the higher dose of AT132. Preliminary reports show the two patients followed a similar clinical course in the weeks before they died.

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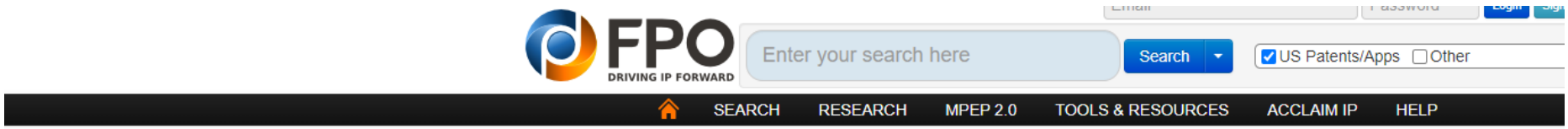

Title: **FORMULATIONS FOR EXTENDING LIFESPAN AND HEALTHSPAN**

Document Type and Number: United States Patent Application 20200188327 **Kind Code:** A1

Abstract: Described herein are compositions for delaying onset or delaying progression of frailty, reversing aging phenotype, extending healthspan, compressing morbidity, increasing lifespan and reducing formation of senescent cells.

What is claimed is:

1. A method of extending lifespan in a subject in need thereof comprising administering to the subject a therapeutically effective amount of berberine, a vitamin A compound, and α-ketoglutarate (AKG).

2. The method of claim 1, wherein berberine, the vitamin A compound and AKG is administered to the subject as a single composition.

3. The method of claim 1, wherein the berberine, the vitamin A compound, and α-ketoglutarate are administered to the subject separately.

4. The method of claim 3, wherein the berberine, the vitamin A compound, and α-ketoglutarate are administered to the subject within a 24 hour period.

5. The method of claim 1, wherein the vitamin A compound is selected from the group consisting of retinol, retinal, retinoic acid, retinyl palmitate, alpha-carotene, beta-carotene, and gamma-carotene.

6. The method of claim 5, wherein the vitamin A compound is retinoic acid or retinyl palmitate.

Frontiers in Genetics topic
Submission deadlines: abstract on 2/08 and manuscript on 29/11

Research Topic

Clinical Evaluation Criteria for Aging and Aging-related Multimorbidity

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About this Research Topic

It is increasingly clear that population aging brings a train of degenerative, malignant and other chronic diseases, such as cancer, type 2 diabetes, chronic obstructive pulmonary disease, neurodegenerative diseases, heart disease, aggravation of infectious diseases. This is also accompanied by other diverse functional, physical and mental impairments. These conditions do not emerge separately from each other, but have related aetiologies and mutually exacerbate each other. This multitude of morbid conditions has been often termed as "multimorbidity" or "co-morbidity". Moreover, it has been suggested that a promising approach to address the entire host of old-age-related morbidities would be by treating their underlying determinative factors – namely fundamental degenerative processes of aging.

Yet, there is currently no agreed method to estimate the direct effects of therapy on tackling the aging process as such, for which there is presently no agreed formal or clinical definition or criteria. Moreover, essentially, there is no agreed formal or clinical definition and criteria for old-age multimorbidity either. Correspondingly, there are no agreed scientifically grounded criteria to select interventions against degenerative aging and old-age multimorbidity or to evaluate their effectiveness. There are clinical methods to diagnose individual age-related diseases and dysfunctions, and assess interventions against those individual diseases and dysfunctions. Yet their integrated evaluation as "aging-related ill health" or "multimorbidity", as well as the selection and evaluation of effective interventions against these conditions, remain as unresolved methodological challenges. As a result, there is no agreed formal conceptual basis for incentivizing industrial development, nor regulatory adoption, of diagnostics and therapies against degenerative aging and aging-related multimorbidity.

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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

Aging research articles

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Selective Neuronal Vulnerability in Alzheimer's Disease: A Network-Based Analysis

A major obstacle to treating Alzheimer's disease (AD) is our lack of understanding of the molecular mechanisms underlying selective neuronal vulnerability, a key characteristic of the disease. Here, we present a framework integrating high-quality neuron-type-specific molecular profiles across the lifetime of the healthy mouse, which we generated using bacTRAP, with postmortem human functional genomics and quantitative genetics data. We demonstrate human-mouse conservation of cellular taxonomy at the molecular level for neurons vulnerable and resistant in AD, identify specific genes and pathways associated with AD neuropathology, and pinpoint a specific functional gene module underlying selective vulnerability, enriched in processes associated with axonal remodeling, and affected by amyloid accumulation and aging. We have made all cell-type-specific profiles and functional networks available at http://alz.princeton.edu. Overall, our study provides a molecular framework for understanding the complex interplay between Aβ, aging, and neurodegeneration within the most vulnerable neurons in AD.

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A brain-wide atlas of synapses across the mouse lifespan

Synapses connect neurons together to form the circuits of the brain and their molecular composition controls innate and learned behavior. We have analyzed the molecular and morphological diversity of five billion excitatory synapses at single-synapse resolution across the mouse brain from birth to old age. A continuum of changes alters synapse composition in all brain regions across the lifespan. Expansion in synapse diversity produces differentiation of brain regions until early adulthood and compositional changes cause dedifferentiation in old age. The spatiotemporal synaptome architecture of the brain potentially accounts for lifespan transitions in intellectual ability, memory, and susceptibility to behavioral disorders.

Alzheimer's Patient Microglia Exhibit Enhanced Aging and Unique Transcriptional Activation

Damage-associated microglia (DAM) profiles observed in Alzheimer's disease (AD)-related mouse models reflect an activation state that could modulate AD risk or progression. To learn whether human AD microglia (HAM) display a similar profile, we develop a method for purifying cell types from frozen cerebrocortical tissues for RNA-seq analysis, allowing better transcriptome coverage than typical single-nucleus RNA-seq approaches. The HAM profile we observe bears little resemblance to the DAM profile. Instead, HAM display an enhanced human aging profile, in addition to other disease-related changes such as APOE upregulation. Analyses of whole-tissue RNA-seq and single-cell/nucleus RNA-seq datasets corroborate our findings and suggest that the lack of DAM response in human microglia occurs specifically in AD tissues, not other neurodegenerative settings. These results, which can be browsed at http://research-pub.gene.com/BrainMyeloidLandscape, provide a genome-wide picture of microglial activation in human AD and highlight considerable differences between mouse models and human disease.

Dynamic Changes of Autophagic Flux Induced by Abeta in the Brain of Postmortem Alzheimer's Disease Patients, Animal Models and Cell Models

Autophagy has been reported to play a dual "double-edged sword" role in the occurrence and development of Alzheimer's disease (AD). To assess the relationship between AD and autophagy, the dynamic changes of autophagic flux in the brain of postmortem AD patients, animal models and cell models were studied. The results showed that autophagosomes (APs) accumulation and expression of lysosomal markers were decreased in the brains of AD patients. In the brain of APP/PS1 double transgenic mice, APs did not accumulate before the formation of SPs but accumulated along with the deposition of SPs, as well as the level of lysosomal markers cathepsin B and Lamp1 protein decreased significantly. In the brains of APP/PS1/LC3 triple - transgenic mice, the number of APs increased with age, but the number of ALs did not increase accordingly. The activation of autophagy is mainly due to the increase in Aβ rather than the overexpression of mutated APP gene. However, both the treatment with exogenous $A\beta_{25-35}$ and the mutation of the endogenous APP gene blocked the fusion of APs with lysosomes and decreased lysosomal functioning in AD model cells, which may be the main mechanism of autophagy dysregulation in AD.

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Reduced proteasome activity in the aging brain results in ribosome stoichiometry loss and aggregation

A progressive loss of protein homeostasis is characteristic of aging and a driver of neurodegeneration. To investigate this process quantitatively, we characterized proteome dynamics during brain aging in the short-lived vertebrate *Nothobranchius furzeri* combining transcriptomics and proteomics. We detected a progressive reduction in the correlation between protein and mRNA , mainly due to post-transcriptional mechanisms that account for over 40% of the age-regulated proteins. These changes cause a progressive loss of stoichiometry in several protein complexes, including ribosomes, which show impaired assembly/disassembly and are enriched in protein aggregates in old brains. Mechanistically, we show that reduction of proteasome activity is an early event during brain aging and is sufficient to induce proteomic signatures of aging and loss of stoichiometry *in vivo* . Using longitudinal transcriptomic data, we show that the magnitude of early life decline in proteasome levels is a major risk factor for mortality. Our work defines causative events in the aging process that can be targeted to prevent loss of protein homeostasis and delay the onset of age-related neurodegeneration.

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Secondary single-cell transcriptomic analysis reveals common molecular signatures of cerebrovascular injury between traumatic brain injury and aging

Xinying Guo, Bangyan Zhang, Fernando Gomez-Pinilla, Fan Gao, Zhen Zhao

Cerebrovascular injury is a common pathological feature of a spectrum of neurological disorders including traumatic brain injury (TBI), stroke, Alzheimer's disease (AD), as well as aging. Vascular manifestations among these conditions are similar indeed, including the breakdown of the blood-brain barrier (BBB). However, whether there is a common molecular mechanism underlying the vascular changes among these conditions remains elusive. Here, we report secondary transcriptomic analysis on cerebrovascular cells based single-cell RNA-seq datasets of mouse models of mild TBI and aging, with a focus on endothelial cells and pericytes. We identify several molecular signatures commonly found between mTBI and aging vasculature, including *Adamts1, Rpl23a, Tmem252, Car4, Serpine2*, and *Ndnf* in endothelial cells, and *Rps29* and *Sepp1* in pericytes. These markers may represent the shared endophenotype of microvascular injury and be considered as cerebrovascular injury responsive genes. Additionally, pathway analysis on differentially expressed genes demonstrated alterations in common pathways between mTBI and aging, including vascular development and extracellular matrix pathways in endothelial cells. Hence, our analysis suggests that cerebrovascular injury triggered by different neurological conditions may share common molecular signatures, which may only be detected at the single-cell transcriptome level.

Transformation of naked mole-rat cells

Fazal Hadi, Yavuz Kulaberoglu, Kyren A. Lazarus, Karsten Bach, Rosemary Ugur, Paul Beattie, Ewan St John Smith ✉ & Walid T. Khaled ✉

Here we developed a number of lentiviral vectors to deliver both of these oncogenes and generated 106 different cell lines from 5 different tissues and 11 different NMRs and show that, in contrast to the previous study[5], NMR cells are susceptible to oncogenic transformation by *SV40LT* and $HRAS^{G12V}$. Our data thus suggest that a non-cell autonomous mechanism underlies the remarkable cancer resistance of NMRs and that identifying this non-cell autonomous mechanism could have important implications for our understanding of cancer development in humans.

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Mapping Drosophila insulin receptor structure to the regulation of aging through analysis of amino acid substitutions

Rochele Yamamoto, Michael Palmer, Helen Koski, Noelle Curtis-Joseph, Marc Tatar

Genetic manipulations of the Drosophila insulin/IGF signaling system slow aging, but it remains unknown how the insulin/IGF receptor acts to modulate lifespan or differentiate this control from that of growth, reproduction and metabolism. With homologous recombination we produced an allelic series of single amino acid substitutions in the fly insulin receptor (InR). Based on emerging biochemical and structural data, we map amino acid substitutions to receptor function to longevity and fecundity. We propose InR mutants generate bias in the process of asymmetric transphosphorylation when the receptor is activated. This induces specific kinase subdomains that modulate lifespan by additive processes, one involving survival costs of reproduction and the other involving reproduction-independent systems of longevity assurance. We identify a mutant in the kinase insert domain that robustly extends lifespan without affecting growth or reproduction, suggesting this element controls aging through unique mechanisms of longevity assurance.

An Insulin-Sensitive Circular RNA That Regulates Lifespan in Drosophila

Carina Marianne Weigelt [1], Rohan Sehgal [1], Luke Stephen Tain [1], Jun Cheng [1], Jacqueline Eßer [1], André Pahl [1], Christoph Dieterich [2], Sebastian Grönke [3], Linda Partridge [4]

Circular RNAs (circRNAs) are abundant and accumulate with age in neurons of diverse species. However, only few circRNAs have been functionally characterized, and their role during aging has not been addressed. Here, we use transcriptome profiling during aging and find that accumulation of circRNAs is slowed down in long-lived insulin mutant flies. Next, we characterize the in vivo function of a circRNA generated by the sulfateless gene (circSfl), which is consistently upregulated, particularly in the brain and muscle, of diverse long-lived insulin mutants. Strikingly, lifespan extension of insulin mutants is dependent on circSfl, and overexpression of circSfl alone is sufficient to extend the lifespan. Moreover, circSfl is translated into a protein that shares the N terminus and potentially some functions with the full-length Sfl protein encoded by the host gene. Our study demonstrates that insulin signaling affects global circRNA accumulation and reveals an important role of circSfl during aging in vivo.

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Genome-wide association studies identify 137 loci for DNA methylation biomarkers of ageing

Biological ageing estimators derived from DNA methylation (DNAm) data are heritable and correlate with morbidity and mortality. Leveraging DNAm and SNP data from >41,000 individuals, we identify 137 genome-wide significant loci (113 novel) from meta-analyses of four epigenetic clocks and epigenetic surrogate markers for granulocyte proportions and plasminogen activator inhibitor 1 levels, respectively. We report strong genetic correlations with longevity and lifestyle factors such as smoking, education, and obesity. Significant associations are observed in polygenic risk score analysis and to a lesser extent in Mendelian randomization analyses. This study illuminates the genetic architecture underlying epigenetic ageing and its shared genetic contributions with lifestyle factors and longevity.

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Common genetic associations between age-related diseases

Handan Melike Donertas, Daniel K Fabian, Matias Fuentealba Valenzuela, Linda Partridge, Janet M Thornton

Age is a common risk factor in many diseases, but the molecular basis for this relationship is elusive. In this study we identified 4 disease clusters from 116 diseases in the UK Biobank data, defined by their age-of-onset profiles, and found that diseases with the same onset profile are genetically more similar, suggesting a common etiology. This similarity was not explained by disease categories, co-occurrences or disease cause-effect relationships. Two of the four disease clusters had an increased risk of occurrence from age 20 and 40 years respectively. They both showed an association with known aging-related genes, yet differed in functional enrichment and evolutionary profiles. We tested mutation accumulation and antagonistic pleiotropy theories of aging and found support for both. We also identified drug candidates for repurposing to target multiple age-dependent diseases with the potential to improve healthspan and alleviate multimorbidity and polypharmacy in the elderly.

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Multifaceted deregulation of gene expression and protein synthesis with age

Aleksandra S. Anisimova, Mark B. Meerson, Maxim V. Gerashchenko, Ivan V. Kulakovskiy, Sergey E. Dmitriev, and Vadim N. Gladyshev

Protein synthesis represents a major metabolic activity of the cell. However, how it is affected by aging and how this in turn impacts cell function remains largely unexplored. To address this question, herein we characterized age-related changes in both the transcriptome and translatome of mouse tissues over the entire life span. We showed that the transcriptome changes govern those in the translatome and are associated with altered expression of genes involved in inflammation, extracellular matrix, and lipid metabolism. We also identified genes that may serve as candidate biomarkers of aging. At the translational level, we uncovered sustained down-regulation of a set of 5′-terminal oligopyrimidine (5′-TOP) transcripts encoding protein synthesis and ribosome biogenesis machinery and regulated by the mTOR pathway. For many of them, ribosome occupancy dropped twofold or even more. Moreover, with age, ribosome coverage gradually decreased in the vicinity of start codons and increased near stop codons, revealing complex age-related changes in the translation process. Taken together, our results reveal systematic and multidimensional deregulation of protein synthesis, showing how this major cellular process declines with age.

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Senolytic CAR T cells reverse senescence-associated pathologies

Cellular senescence is characterized by stable cell-cycle arrest and a secretory program that modulates the tissue microenvironment[1,2]. Physiologically, senescence serves as a tumour-suppressive mechanism that prevents the expansion of premalignant cells[3,4] and has a beneficial role in wound-healing responses[5,6]. Pathologically, the aberrant accumulation of senescent cells generates an inflammatory milieu that leads to chronic tissue damage and contributes to diseases such as liver and lung fibrosis, atherosclerosis, diabetes and osteoarthritis[1,7]. Accordingly, eliminating senescent cells from damaged tissues in mice ameliorates the symptoms of these pathologies and even promotes longevity[1,2,8,9,10]. Here we test the therapeutic concept that chimeric antigen receptor (CAR) T cells that target senescent cells can be effective senolytic agents. We identify the urokinase-type plasminogen activator receptor (uPAR)[11] as a cell-surface protein that is broadly induced during senescence and show that uPAR-specific CAR T cells efficiently ablate senescent cells in vitro and in vivo. CAR T cells that target uPAR extend the survival of mice with lung adenocarcinoma that are treated with a senescence-inducing combination of drugs, and restore tissue homeostasis in mice in which liver fibrosis is induced chemically or by diet. These results establish the therapeutic potential of senolytic CAR T cells for senescence-associated diseases.

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The Senolytic Drug Navitoclax (ABT-263) Causes Trabecular Bone Loss and Impaired Osteoprogenitor Function in Aged Mice

Senescence is a cellular defense mechanism that helps cells prevent acquired damage, but chronic senescence, as in aging, can contribute to the development of age-related tissue dysfunction and disease. Previous studies clearly show that removal of senescent cells can help prevent tissue dysfunction and extend healthspan during aging. Senescence increases with age in the skeletal system, and selective depletion of senescent cells or inhibition of their senescence-associated secretory phenotype (SASP) has been reported to maintain or improve bone mass in aged mice. This suggests that promoting the selective removal of senescent cells, via the use of senolytic agents, can be beneficial in the treatment of aging-related bone loss and osteoporosis. Navitoclax (also known as ABT-263) is a chemotherapeutic drug reported to effectively clear senescent hematopoietic stem cells, muscle stem cells, and mesenchymal stromal cells in previous studies, but its *in vivo* effects on bone mass had not yet been reported. Therefore, the purpose of this study was to assess the effects of short-term navitoclax treatment on bone mass and osteoprogenitor function in old mice. Aged (24 month old) male and female mice were treated with navitoclax (50 mg/kg body mass daily) for 2 weeks. Surprisingly, despite decreasing senescent cell burden, navitoclax treatment decreased trabecular bone volume fraction in aged female and male mice (−60.1% females, −45.6% males), and BMSC-derived osteoblasts from the navitoclax treated mice were impaired in their ability to produce a mineralized matrix (−88% females, −83% males). Moreover, *in vitro* administration of navitoclax decreased BMSC colony formation and calcified matrix production by aged BMSC-derived osteoblasts, similar to effects seen with the primary BMSC from the animals treated *in vivo*. Navitoclax also significantly increased metrics of cytotoxicity in both male and female osteogenic cultures (+1.0 to +11.3 fold). Taken together, these results suggest a potentially harmful effect of navitoclax on skeletal-lineage cells that should be explored further to definitively assess navitoclax's potential (or risk) as a therapeutic agent for combatting age-related musculoskeletal dysfunction and bone loss.

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Sentinel $p16^{INK4a}$+ cells in the basement membrane form a reparative niche in the lung

Senescent cells are recognized drivers of aging-related decline in organ function, but deciphering the biology of senescence *in vivo* has been hindered by the paucity of tools to track and isolate senescent cells in tissues[1–4]. Deleting senescent cells from transgenic murine models have demonstrated therapeutic benefits in numerous age-related diseases[5–11], but the identity, behavior, and function of the senescent cells deleted *in vivo* remain elusive. We engineered an ultra-sensitive reporter of $p16^{INK4a}$, a biomarker of senescence[12], to isolate and track $p16^{INK4a}$+ cells *in vivo*. Surprisingly, $p16^{INK4a}$+ mesenchymal cells appear in the basement membrane adjacent to epithelial progenitors in the lung shortly after birth, and these cells demonstrate senescent characteristics *in vivo* and *ex vivo*. Transcriptomic analysis of $p16^{INK4a}$+ mesenchymal cells from non-aged lungs demonstrates a transition to a secretory phenotype upon airway epithelial injury. Heterotypic 3D organoid assays show that injured $p16^{INK4a}$+ mesenchymal cells enhance epithelial progenitor proliferation, and we identified EREG as a novel airway progenitor mitogen produced by the secretory $p16^{INK4a}$+ mesenchymal cells. Mesenchymal-specific deletion of the $p16^{INK4a}$ gene abrogates features of senescence *in vivo*, but also attenuates normal epithelial repair. Thus, $p16^{INK4a}$+ mesenchymal cells can act as sentinels for the airway epithelial stem cell niche, poised to transition to a senescence-associated secretory phenotype to support barrier repair. Our data identify possible cellular targets *in vivo* for a rapidly growing list of senolytic therapies, but also raises important questions about the hidden cost of targeting senescent cells present in normal organs.

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The senescence-associated secretome as an indicator of age and medical risk

Marissa J. Schafer,[1,2] Xu Zhang,[1,2] Amanika Kumar,[3] Elizabeth J. Atkinson,[4] Yi Zhu,[1] Sarah Jachim,[1] Daniel L. Mazula,[1] Ashley K. Brown,[1] Michelle Berning,[1] Zaira Aversa,[1,2] Brian Kotajarvi,[5] Charles J. Bruce,[6] Kevin L. Greason,[7] Rakesh M. Suri,[7,8] Russell P. Tracy,[9] Steven R. Cummings,[10,11] Thomas A. White,[1] and Nathan K. LeBrasseur[1,2]

First published June 18, 2020 - More info

Abstract

Produced by senescent cells, the senescence-associated secretory phenotype (SASP) is a potential driver of age-related dysfunction. We tested whether circulating concentrations of SASP proteins reflect age and medical risk in humans. We first screened senescent endothelial cells, fibroblasts, preadipocytes, epithelial cells, and myoblasts to identify candidates for human profiling. We then tested associations between circulating SASP proteins and clinical data from individuals throughout the life span and older adults undergoing surgery for prevalent but distinct age-related diseases. A community-based sample of people aged 20–90 years (retrospective cross-sectional) was studied to test associations between circulating SASP factors and chronological age. A subset of this cohort aged 60–90 years and separate cohorts of older adults undergoing surgery for severe aortic stenosis (prospective longitudinal) or ovarian cancer (prospective case-control) were studied to assess relationships between circulating concentrations of SASP proteins and biological age (determined by the accumulation of age-related health deficits) and/or postsurgical outcomes. We showed that SASP proteins were positively associated with age, frailty, and adverse postsurgery outcomes. A panel of 7 SASP factors composed of growth differentiation factor 15 (GDF15), TNF receptor superfamily member 6 (FAS), osteopontin (OPN), TNF receptor 1 (TNFR1), ACTIVIN A, chemokine (C-C motif) ligand 3 (CCL3), and IL-15 predicted adverse events markedly better than a single SASP protein or age. Our findings suggest that the circulating SASP may serve as a clinically useful candidate biomarker of age-related health and a powerful tool for interventional human studies.

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Senescent cell death as an aging resistance mechanism in naked mole-rat

Naked mole-rats (NMRs) are the longest-lived rodents, showing minimal aging phenotypes. An unsolved paradox is that NMRs exhibit low intracellular anti-oxidant defence despite minimal aging. Here, we explained a link between these "contradicting" features by a phenomenon termed "senescent cell death (SCD)"—Senescence induced cell death in NMR cells due to their inherent vulnerability to reactive oxygen species and unique metabolic system. In NMR skin, we observed few senescent cells during aging or after ultraviolet irradiation, suggesting suppression of senescent cell accumulation in NMR tissue. We discovered that senescent NMR-fibroblasts induce SCD through retinoblastoma protein activation accompanied by autophagy dysregulation, increased oxidative damage and accelerated H_2O_2-releasing metabolic pathways. During senescence, NMR cells showed resistance to metabolic remodelling unlike mice. Our findings provide mechanistic insights into how extraordinary aging resistance is accomplished in NMR. This will contribute to the development of senolytic drugs to regulate age-related diseases.

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Dysfunctional telomeres trigger cellular senescence mediated by cyclic GMP-AMP synthase

Defective DNA damage response (DDR) signaling is a common mechanism that initiates and maintains the cellular senescence phenotype. Dysfunctional telomeres activate DDR signaling, genomic instability, and cellular senescence, but the links among these events remains unclear. Here, using an array of biochemical and imaging techniques, including a highly regulatable CRISPR/Cas9 strategy to induce DNA double-strand breaks specifically in the telomeres, chromatin immunoprecipitation, telomere immunofluorescence, fluorescence in situ hybridization (FISH), micronuclei imaging, and the telomere shortest length assay (TeSLA), we show that chromosome mis-segregation due to imperfect DDR signaling in response to dysfunctional telomeres creates a preponderance of chromatin fragments in the cytosol, which leads to a premature senescence phenotype. We found that this phenomenon is caused not by telomere shortening, but by cyclic GMP–AMP synthase (cGAS) recognizing cytosolic chromatin fragments and then activating the stimulator of interferon genes (STING) cytosolic DNA-sensing pathway and downstream interferon signaling. Significantly, genetic and pharmacological manipulation of cGAS not only attenuated immune signaling, but also prevented premature cellular senescence in response to dysfunctional telomeres. The findings of our study uncover a cellular intrinsic mechanism involving the cGAS-mediated cytosolic self-DNA–sensing pathway that initiates premature senescence independently of telomere shortening.

The Human Telomeric Proteome During Telomere Replication

Telomere shortening can cause detrimental diseases and contribute to aging. It occurs due to the end replication problem in cells lacking telomerase. Furthermore, recent studies revealed that telomere shortening can be attributed to difficulties of the semi-conservative DNA replication machinery to replicate through the bulk of telomeric DNA repeats. To investigate telomere replication in a comprehensive manner, we develop QTIP-iPOND, which enables purification of proteins that associate with telomeres specifically during replication. We identify in addition to the core replisome a large number of proteins that associate with telomere replication forks and validate their importance. We find that POT1 is depleted, whereas histone H1 is specifically enriched, at telomere replication forks. Our work reveals the dynamic changes of the telomeric proteome during replication, providing a valuable resource of telomere replication proteins. To our knowledge, this is the first study that examines the replisome at a specific region of the genome.

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Persistent telomere cohesion protects aged cells from premature senescence

Human telomeres are bound by the telomere repeat binding proteins TRF1 and TRF2. Telomere shortening in human cells leads to a DNA damage response that signals replicative senescence. While insufficient loading of TRF2 at shortened telomeres contributes to the DNA damage response in senescence, the contribution of TRF1 to senescence induction has not been determined. Here we show that counter to TRF2 deficiency-mediated induction of DNA damage, TRF1 deficiency serves a protective role to limit induction of DNA damage induced by subtelomere recombination. Shortened telomeres recruit insufficient TRF1 and as a consequence inadequate tankyrase 1 to resolve sister telomere cohesion. Our findings suggest that the persistent cohesion protects short telomeres from inappropriate recombination. Ultimately, in the final division, telomeres are no longer able to maintain cohesion and subtelomere copying ensues. Thus, the gradual loss of TRF1 and concomitant persistent cohesion that occurs with telomere shortening ensures a measured approach to replicative senescence.

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Life-long telomere attrition predicts health and lifespan in a large mammal

Telomere length measured in blood cells is predictive of subsequent adult health and survival across a range of vertebrate species. However, we currently do not know whether such associations result from among-individual differences in telomere length determined genetically or by environmental factors early in life, or from differences in the rate of telomere attrition over the course of life. Here, we measured relative leukocyte telomere length (RLTL) multiple times across the entire lifespan of dairy cattle in a research population that is closely monitored for health and milk production and where individuals are only culled in response to health issues and less due to poor milk production than on purely commercial farms. Our results clearly show that the average amount of telomere attrition over an individual's life, not their average or early life telomere length predicted when an individual was culled. Within-individual telomere length attrition could reflect environmental or physiological insults which may accumulate to predict individual health-span. We also show that animals with more telomere attrition in their first year of life were culled at a younger age, indicating that early life stressors may have a prolonged effect on adult life.

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Immunosenescence and its influence on reproduction in a long-lived vertebrate

Jessica M. Judson, Dawn M. Reding, Anne M. Bronikowski

Immunosenescence is a well-known phenomenon in mammal systems, but its relevance in other long-lived vertebrates is less understood. Further, the influence of age and reproductive effort on immune function in long-lived species can be challenging to assess, as long-term data are scarce and it is often difficult to sample the oldest age classes. We used the painted turtle (*Chrysemys picta*) to test hypotheses of immunosenescence and a trade-off between reproductive output and immune function in a population of a long-lived vertebrate that has been monitored for over 30 years. These long-term data were utilized to employ a unique approach of aging turtles with mark–recapture data and population-specific growth modeling to obtain more accurate estimates of age. We analyzed natural antibodies, lysis ability and bactericidal competence in 126 individuals from 1 to 33 years of age captured during May and June 2011. Older turtles exhibited greater natural antibody levels than young individuals. Young females with large clutches exhibited greater lysis ability, while older females with large clutches had decreased lysis ability, suggesting a trade-off between reproductive output and immune function conditional upon age. However, bactericidal competence increased later in the nesting season for older females. Our study rejects the hypothesis of immunosenescence in a long-lived turtle, despite evidence of actuarial and reproductive senescence in this population. Additionally, we detected mixed evidence for a trade-off between reproduction and immune health.

T cells with dysfunctional mitochondria induce multimorbidity and premature senescence

The effect of immunometabolism on age-associated diseases remains uncertain. In this work, we show that T cells with dysfunctional mitochondria owing to mitochondrial transcription factor A (TFAM) deficiency act as accelerators of senescence. In mice, these cells instigate multiple aging-related features, including metabolic, cognitive, physical, and cardiovascular alterations, which together result in premature death. T cell metabolic failure induces the accumulation of circulating cytokines, which resembles the chronic inflammation that is characteristic of aging ("inflammaging"). This cytokine storm itself acts as a systemic inducer of senescence. Blocking tumor necrosis factor–α signaling or preventing senescence with nicotinamide adenine dinucleotide precursors partially rescues premature aging in mice with *Tfam*-deficient T cells. Thus, T cells can regulate organismal fitness and life span, which highlights the importance of tight immunometabolic control in both aging and the onset of age-associated diseases.

Age-related changes in the physical properties, cross-linking, and glycation of collagen from mouse tail tendon

Collagen is a structural protein whose internal cross-linking critically determines the properties and functions of connective tissue. Knowing how the cross-linking of collagen changes with age is key to understanding why the mechanical properties of tissues change over a lifetime. The current scientific consensus is that collagen cross-linking increases with age and that this increase leads to tendon stiffening. Here, we show that this view should be reconsidered. Using MS-based analyses, we demonstrate that during aging of healthy C57BL/6 mice, the overall levels of collagen cross-linking in tail tendon decrease with age. However, the levels of lysine glycation in collagen, which is not considered a cross-link, increased dramatically with age. We found that in 16-week-old diabetic db/db mice, glycation reaches levels similar to those observed in 98-week-old C57BL/6 mice, while the other cross-links typical of tendon collagen either decreased or remained the same as those observed in 20 week old WT mice. These results, combined with findings from mechanical testing of tendons from these mice, indicate that overall collagen cross-linking in mouse tendon decreases with age. Our findings also reveal that lysine glycation appears to be an important factor that contributes to tendon stiffening with age and in diabetes.

Mechanical Stretching Changes Cross-Linking and Glycation Levels in the Collagen of Mouse Tail Tendon

Melanie Stammers [1], Izabella S Niewczas [1], Anne Segonds-Pichon [1], Jonathan Clark [1]

Collagen I is a major tendon protein whose polypeptide chains are linked by covalent cross-links. It is unknown how the cross-linking contributes to the mechanical properties of tendon or whether cross-linking changes in response to stretching or relaxation. Since their discovery, imine bonds within collagen have been recognized as being important in both cross-link formation and collagen structure. They are often described as acidic or thermally labile, but no evidence is available from direct measurements of cross-link levels whether these bonds contribute to the mechanical properties of collagen. Here, we used MS to analyze these imine bonds after reduction with sodium borohydride while under tension and found that their levels are altered in stretched tendon. We studied the changes in cross-link bonding in tail tendon from 11-week-old C57Bl/6 mice at 4% physical strain, at 10% strain, and at breaking point. The cross-links hydroxy-lysino-norleucine (HLNL), dihydroxy-lysino-norleucine (DHLNL), and lysino-norleucine (LNL) increased or decreased depending on the specific cross-link and amount of mechanical strain. We also noted a decrease in glycated lysine residues in collagen, indicating that the imine formed between circulating glucose and lysine is also stress-labile. We also carried out mechanical testing, including cyclic testing at 4% strain, stress relaxation tests, and stress-strain profiles taken at breaking point, both with and without sodium borohydride reduction. The results from both the MS studies and mechanical testing provide insights into the chemical changes during tendon stretching and directly link these chemical changes to functional collagen properties.

It's all in our skin—*Skin autofluorescence*—A promising outcome predictor in cardiac surgery: A single centre cohort study

Background

The optimum risk score determining perioperative mortality and morbidity in cardiac surgery remains debated. Advanced glycation end products (AGEs) derived from glycaemic and oxidative stress accumulate to a comparable amount in skin and the cardiovascular system leading to a decline in organ function. We aimed to study the association between AGE accumulation measured as skin autofluorescence (sAF) and the outcome of cardiac surgery patients.

Methods

Between April 2008 and November 2016, data from 758 consecutive patients undergoing coronary artery bypass grafting, aortic valve replacement or a combined procedure were analyzed. Skin autofluorescence was measured using an autofluorescence reader. Beside mortality, for the combined categorical morbidity outcome of each patient failure of the cardiac-, pulmonary-, renal- and cerebral system, as well as reoperation and wound healing disorders were counted. Patients without or with only one of the outcomes were assigned zero points whereas more than one outcome failure resulted in one point. Odds ratios (ORs) were estimated in multivariable logistic regression analysis with other preoperative parameters and the established cardiac surgery risk score systems EuroSCORE II and STS score.

Results

Skin autofluorescence as non-invasive marker of tissue glycation provided the best prognostic value in identifying patients with major morbidity risks after cardiac surgery (OR = 3.13; 95%CI 2.16–4.54). With respect to mortality prediction the STS score (OR = 1.24; 95%CI 1.03–1.5) was superior compared to the EuroSCORE II (OR = 1.17: 95%CI 0.96–1.43), but not superior when compared to sAF (OR = 6.04; 95%CI 2.44–14.95).

Conclusion

This finding suggests that skin autofluorescence is a good biomarker candidate to assess the perioperative risk of patients in cardiac surgery. Since the EuroSCORE does not contain a morbidity component, in our view further sAF measurement is an option.

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Trimethylamine-N-Oxide Promotes Age-Related Vascular Oxidative Stress and Endothelial Dysfunction in Mice and Healthy Humans

Vienna E. Brunt, Rachel A. Gioscia-Ryan, Abigail G. Casso, Nicholas S. VanDongen, Brian P. Ziemba, Zachary J. Sapinsley, James J. Richey, Melanie C. Zigler, Andrew P. Neilson, Kevin P. Davy, Douglas R. Seals

Age-related vascular endothelial dysfunction is a major antecedent to cardiovascular diseases. We investigated whether increased circulating levels of the gut microbiome-generated metabolite trimethylamine-N-oxide induces endothelial dysfunction with aging. In healthy humans, plasma trimethylamine-N-oxide was higher in middle-aged/older (64±7 years) versus young (22±2 years) adults (6.5±0.7 versus 1.6±0.2 μmol/L) and inversely related to brachial artery flow-mediated dilation (r^2=0.29, P<0.00001). In young mice, 6 months of dietary supplementation with trimethylamine-N-oxide induced an aging-like impairment in carotid artery endothelium-dependent dilation to acetylcholine versus control feeding (peak dilation: 79±3% versus 95±3%, P<0.01). This impairment was accompanied by increased vascular nitrotyrosine, a marker of oxidative stress, and reversed by the superoxide dismutase mimetic 4-hydroxy-2,2,6,6-tetramethylpiperidin-1-oxyl. Trimethylamine-N-oxide supplementation also reduced activation of endothelial nitric oxide synthase and impaired nitric oxide-mediated dilation, as assessed with the nitric oxide synthase inhibitor L-NAME (N^G-nitro-L-arginine methyl ester). Acute incubation of carotid arteries with trimethylamine-N-oxide recapitulated these events. Next, treatment with 3,3-dimethyl-1-butanol for 8 to 10 weeks to suppress trimethylamine-N-oxide selectively improved endothelium-dependent dilation in old mice to young levels (peak: 90±2%) by normalizing vascular superoxide production, restoring nitric oxide-mediated dilation, and ameliorating superoxide-related suppression of endothelium-dependent dilation. Lastly, among healthy middle-aged/older adults, higher plasma trimethylamine-N-oxide was associated with greater nitrotyrosine abundance in biopsied endothelial cells, and infusion of the antioxidant ascorbic acid restored flow-mediated dilation to young levels, indicating tonic oxidative stress-related suppression of endothelial function with higher circulating trimethylamine-N-oxide. Using multiple experimental approaches in mice and humans, we demonstrate a clear role of trimethylamine-N-oxide in promoting age-related endothelial dysfunction via oxidative stress, which may have implications for prevention of cardiovascular diseases.

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Transcriptomic Landscape Profiling of Metformin-Treated Healthy Mice: Implication for Potential Hypertension Risk When Prophylactically Used

Recently, the first-line anti-diabetic drug metformin shows versatile protective effects against several diseases and is potentially prescribed to healthy individual for prophylactic use against ageing or other pathophysiological processes. However, for healthy individuals, it remains unclear what effects metformin treatment will induce on their bodies. A systematic profiling of the molecular landscape of metformin treatment is expected to provide crucial implications for this issue. Here, we delineated the first transcriptomic landscape induced by metformin in 10 tissues (aorta, brown adipose, brain, eye, heart, liver, kidney, skeletal muscle, stomach and testis) of healthy mice by using RNA-sequencing technique. A comprehensive computational analysis was performed. The overrepresentation of cardiovascular disease-related gene sets, positive correlation with hypertension-related transcriptomic signatures and the associations of drugs with hypertensive side effect together indicate that although metformin does exert various beneficial effects, it would also increase the risk of hypertension in healthy mice. This prediction was experimentally validated by an independent animal experiments. Together, this study provided important resource necessary for investigating metformin's beneficial/deleterious effects on various healthy tissues, when it is potentially prescribed to healthy individual for prophylactic use.

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Metformin Prescription Associated With Reduced AAA Growth Rate and Reduced Chemokine Expression in a Swedish Cohort

Objective: Recent reports suggest that the negative association between diabetes mellitus and abdominal aortic aneurysm (AAA) may be driven by metformin, the world's most common antidiabetic drug, rather than diabetes per se. We sought to investigate the association between AAA growth rate, chemokine profile and metformin prescription in a contemporary Swedish cohort.

Methods: Patients under surveillance for small AAA were identified at four Swedish vascular centers with active AAA screening programs. Annual AAA growth rate, medical history and prescribed medications were recorded for linear regression analysis. In a subset of patients with AAA and controls without AAA or diabetes, plasma samples were available and analyzed for forty inflammatory chemokines.

Results: 526 patients were included for AAA growth analysis; 428 without type two diabetes mellitus (T2DM), 65 with T2DM and metformin prescription and 33 with T2DM but without metformin prescription. Patients were included form 2005 to 2017 with mean follow up of 3.2 (1.7) years and median annual AAA growth rate 1.6 mm, range -4.8 to 15.4 mm. Mean (SD) annual AAA growth rates were 2.3 (2.2) mm in non-T2DM patients versus 1.1 (1.1) mm in T2DM patients with metformin prescription and 1.6 (1.4) mm amongst those with T2DM without metformin prescription. With non-T2DM patients as reference in an unadjusted and two adjusted models, metformin prescription was significantly associated with reduced AAA growth rate ($p<0.001$, $p=0.005$ and $p=0.024$ respectively), but not T2DM without metformin prescription ($p=0.137$ $p=0.331$ and $p=0.479$ respectively). Amongst 240 patients with AAA (152 without T2DM, 51 with T2DM and metformin and 37 with T2DM without metformin) and 59 without AAA or T2DM, metformin prescription was associated with reduced expression of chemokines representing all classes of leukocytes.

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Smooth Muscle Sirtuin 1 Blocks Thoracic Aortic Aneurysm/Dissection Development in Mice

Purpose: Advancing age is the major risk factor for thoracic aortic aneurysm/dissection (TAAD). However, the causative link between age-related molecules and TAAD remains elusive. Here, we investigated the role of Sirtuin 1 (SIRT1, also known as class III histone deacetylase), the best studied member of the longevity-related Sirtuin family, in TAAD development in vivo.

Methods: We used male smooth muscle-specific SIRT1 transgenic (ST-Tg) mice, smooth muscle-specific SIRT1 knockout (ST-KO) mice, and their wild-type (WT) littermates on a C57BL/6J background to establish a TAAD model induced by oral administration of 3-aminopropionitrile fumarate (BAPN). We analyzed the incidence and fatality rates of TAAD in the groups. We examined matrix metallopeptidase 2 (MMP2) and MMP9 expression in aortas or cultured A7r5 cells via western blotting and real-time polymerase chain reaction (PCR). We performed chromatin immunoprecipitation (ChIP) to clarify the epigenetic mechanism of SIRT1-regulated MMP2 expression in vascular smooth muscle cells (VSMCs).

Results: BAPN treatment markedly increased the incidence of TAAD in WT mice but caused less disease in ST-Tg mice. Moreover, ST-KO mice had the highest BAPN-induced TAAD fatality rate of all the groups. Mechanistically, SIRT1 overexpression resulted in lower MMP2 and MMP9 expression after BAPN treatment in both mouse aortas and cultured A7r5 cells. The downregulation of BAPN-induced MMP2 expression by SIRT1 was mediated by deacetylation of histone H3 lysine 9 (H3K9) on the Mmp2 promoter in the A7r5 cells.

Conclusion: Our findings suggest that SIRT1 expression in SMCs protects against TAAD and could be a novel therapeutic target for TAAD management.

Lifelong SIRT-1 Overexpression Attenuates Large Artery Stiffening With Advancing Age

Daniel R Machin [1], Yauling Auduong [1], Venkateswara R Gogulamudi [1], Yu Liu [1], Md Torikul Islam [2], Lisa A Lesniewski [1 2 3], Anthony J Donato [1 2 4 3]

Advanced age is accompanied by aortic stiffening that is associated with decreased vascular expression of sirtuin-1 (SIRT-1). Interventions that increase SIRT-1 expression also lower age-related aortic stiffness. Therefore, we sought to determine if lifelong SIRT-1 overexpression would attenuate age-related aortic stiffening. Aortic pulse wave velocity (PWV) was assessed from 3-24 months in SIRT-1 transgenic overexpressing ($SIRT^{TG}$) and wild-type (WT) mice. To determine the role of aortic structural changes on aortic stiffening, histological assessment of aortic wall characteristics was performed. Across the age range (3-24 mo), PWV was 8-17% lower in $SIRT^{TG}$ vs. WT ($P<0.05$). Moreover, the slope of age-related aortic stiffening was lower in $SIRT^{TG}$ vs. WT (2.1±0.2 vs. 3.8±0.3 cm/sec/mo, respectively). Aortic elastin decreased with advancing age in WT ($P<0.05$ old vs. young WT), but was maintained in $SIRT^{TG}$ mice ($P>0.05$). There was an age-related increase in aortic collagen, advanced glycation end products, and calcification in WT ($P<0.05$ old vs. young WT). However, this did not occur in $SIRT^{TG}$ ($P>0.05$). These findings indicate that lifelong SIRT-1 overexpression attenuates age-related aortic stiffening. These functional data are complemented by histological assessment, demonstrating that the deleterious changes to the aortic wall that normally occur with advancing age are prevented in $SIRT^{TG}$ mice.

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In Vivo Quasi-Elastic Light Scattering Eye Scanner Detects Molecular Aging in Humans FREE

The absence of clinical tools to evaluate individual variation in the pace of aging represents a major impediment to understanding aging and maximizing health throughout life. The human lens is an ideal tissue for quantitative assessment of molecular aging in vivo. Long-lived proteins in lens fiber cells are expressed during fetal life, do not undergo turnover, accumulate molecular alterations throughout life, and are optically accessible in vivo. We used quasi-elastic light scattering (QLS) to measure age-dependent signals in lenses of healthy human subjects. Age-dependent QLS signal changes detected in vivo recapitulated time-dependent changes in hydrodynamic radius, protein polydispersity, and supramolecular order of human lens proteins during long-term incubation (~1 year) and in response to sustained oxidation (~2.5 months) in vitro. Our findings demonstrate that QLS analysis of human lens proteins provides a practical technique for noninvasive assessment of molecular aging in vivo.

The Mitochondrial Derived Peptide Humanin Is a Regulator of Lifespan and Healthspan

Humanin is a member of a new family of peptides that are encoded by short open reading frames within the mitochondrial genome. It is conserved in animals and is both neuroprotective and cytoprotective. Here we report that in *C. elegans* the overexpression of humanin is sufficient to increase lifespan, dependent on *daf-16/Foxo*. Humanin transgenic mice have many phenotypes that overlap with the worm phenotypes and, similar to exogenous humanin treatment, have increased protection against toxic insults. Treating middle-aged mice twice weekly with the potent humanin analogue HNG, humanin improves metabolic healthspan parameters and reduces inflammatory markers. In multiple species, humanin levels generally decline with age, but here we show that levels are surprisingly stable in the naked mole-rat, a model of negligible senescence. Furthermore, in children of centenarians, who are more likely to become centenarians themselves, circulating humanin levels are much greater than age-matched control subjects. Further linking humanin to healthspan, we observe that humanin levels are decreased in human diseases such as Alzheimer's disease and MELAS (Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-like episodes). Together, these studies are the first to demonstrate that humanin is linked to improved healthspan and increased lifespan.

Heales
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Gray whale transcriptome reveals longevity adaptations associated with DNA repair and ubiquitination

Dmitri Toren, Anton Kulaga, Mineshbhai Jethva, Eitan Rubin, Anastasia V. Snezhkina, Anna V. Kudryavtseva, Dmitry Nowicki, Robi Tacutu, Alexey A. Moskalev ✉, Vadim E. Fraifeld ✉

One important question in aging research is how differences in genomics and transcriptomics determine the maximum lifespan in various species. Despite recent progress, much is still unclear on the topic, partly due to the lack of samples in nonmodel organisms and due to challenges in direct comparisons of transcriptomes from different species. The novel ranking-based method that we employ here is used to analyze gene expression in the gray whale and compare its de novo assembled transcriptome with that of other long- and short-lived mammals. Gray whales are among the top 1% longest-lived mammals. Despite the extreme environment, or maybe due to a remarkable adaptation to its habitat (intermittent hypoxia, Arctic water, and high pressure), gray whales reach at least the age of 77 years. In this work, we show that long-lived mammals share common gene expression patterns between themselves, including high expression of DNA maintenance and repair, ubiquitination, apoptosis, and immune responses. Additionally, the level of expression for gray whale orthologs of pro- and anti-longevity genes found in model organisms is in support of their alleged role and direction in lifespan determination. Remarkably, among highly expressed pro-longevity genes many are stress-related, reflecting an adaptation to extreme environmental conditions. The conducted analysis suggests that the gray whale potentially possesses high resistance to cancer and stress, at least in part ensuring its longevity. This new transcriptome assembly also provides important resources to support the efforts of maintaining the endangered population of gray whales.

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Rhesus macaques as a tractable physiological model of human ageing

Research in the basic biology of ageing is increasingly identifying mechanisms and modifiers of ageing in short-lived organisms such as worms and mice. The ultimate goal of such work is to improve human health, particularly in the growing segment of the population surviving into old age. Thus far, few interventions have robustly transcended species boundaries in the laboratory, suggesting that changes in approach are needed to avoid costly failures in translational human research. In this review, we discuss both well-established and alternative model organisms for ageing research and outline how research in nonhuman primates is sorely needed, first, to translate findings from shorter-lived organisms to humans, and second, to understand key aspects of ageing that are unique to primate biology. We focus on rhesus macaques as a particularly promising model organism for ageing research due to their social and physiological similarity to humans as well as the existence of key resources that have been developed for this species. As a case study, we compare gene regulatory signatures of ageing in the peripheral immune system between humans and rhesus macaques from a free-ranging study population in Cayo Santiago. We show that both mRNA expression and DNA methylation signatures of immune ageing are broadly shared between macaques and humans, indicating strong conservation of the trajectory of ageing in the immune system. We conclude with a review of key issues in the biology of ageing for which macaques and other nonhuman primates may uniquely contribute valuable insights, including the effects of social gradients on health and ageing. We anticipate that continuing research in rhesus macaques and other nonhuman primates will play a critical role in conjunction with model organism and human biodemographic research in ultimately improving translational outcomes and extending health and longevity in our ageing population.

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The genome of North American beaver provides insights into the mechanisms of its longevity and cancer resistance

The North American beaver (Castor canadensis) is an exceptionally long-lived and cancer-resistant rodent species, and thus an excellent model organism for comparative genomic studies of longevity. Here, we utilize a significantly improved beaver genome assembly to assess evolutionary changes in gene coding sequences, copy number, and expression. We found that the beaver Aldh1a1, a stem cell marker gene encoding an enzyme required for detoxification of ethanol and aldehydes, is expanded (~10 copies vs. two in mouse and one in human). We also show that the beaver cells are more resistant to ethanol, and beaver liver extracts show higher ability to metabolize aldehydes than the mouse samples. Furthermore, Hpgd, a tumor suppressor gene, is uniquely duplicated in the beaver among rodents. Our evolutionary analysis identified beaver genes under positive selection which are associated with tumor suppression and longevity. Genes involved in lipid metabolism show positive selection signals, changes in copy number and altered gene expression in beavers. Several genes involved in DNA repair showed a higher expression in beavers which is consistent with the trend observed in other long-lived mammals. In summary, we identified several genes that likely contribute to beaver longevity and cancer resistance, including increased ability to detoxify aldehydes, enhanced tumor suppression and DNA repair, and altered lipid metabolism.

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Human Gut Microbiome Aging Clock Based on Taxonomic Profiling and Deep Learning

The human gut microbiome is a complex ecosystem that both affects and is affected by its host status. Previous metagenomic analyses of gut microflora revealed associations between specific microbes and host age. Nonetheless there was no reliable way to tell a host's age based on the gut community composition. Here we developed a method of predicting hosts' age based on microflora taxonomic profiles using a cross-study dataset and deep learning. Our best model has an architecture of a deep neural network that achieves the mean absolute error of 5.91 years when tested on external data. We further advance a procedure for inferring the role of particular microbes during human aging and defining them as potential aging biomarkers. The described intestinal clock represents a unique quantitative model of gut microflora aging and provides a starting point for building host aging and gut community succession into a single narrative.

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Healthy aging interventions reduce non-coding repetitive element transcripts

Devin Wahl, Alyssa N. Cavalier, Meghan Smith, Douglas R. Seals, Thomas J. LaRocca

Transcripts from non-coding repetitive elements (RE) in the genome may be involved in aging. However, they are often ignored in transcriptome studies on healthspan and lifespan, and their role in healthy aging interventions has not been characterized. Here, we analyze RE in RNA-seq datasets from mice subjected to robust healthspan- and lifespan-increasing interventions including calorie restriction, rapamycin, acarbose, 17-α-estradiol, and Protandim. We also examine RE transcripts in long-lived transgenic mice, and in mice subjected to high-fat diet, and we use RNA-seq to investigate the influence of aerobic exercise on RE transcripts with aging in humans. We find that: 1) healthy aging interventions/behaviors globally reduce RE transcripts, whereas aging and age-accelerating treatments increase RE expression; and 2) reduced RE expression with healthy aging interventions is associated with biological/physiological processes mechanistically linked with aging. Thus, RE transcript dysregulation and suppression are likely novel mechanisms underlying aging and healthy aging interventions, respectively.

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Aging interacts with tumor biology to produce major changes in the immune tumor microenvironment

Advanced age is strongly correlated with both increased cancer incidence and general immune decline. The immune tumor microenvironment (ITME) has been established as an important prognostic of both therapeutic efficacy and overall patient survival. Thus, age-related immune decline is an important consideration for the treatment of a large subset of cancer patients. Current studies of aging-related immune alterations are predominantly performed on non-cancerous tissue, requiring additional study into the effects of age on tumor immune infiltration. We leverage large scale transcriptional data sets from The Cancer Genome Atlas and the Genotype-Tissue Expression project to distinguish normal age-related immune alterations from age-related changes in tumor immune infiltration. We demonstrate that while there is overlap between the normal immune aging phenotype and that of the ITME, there are several changes in immune cell abundance that are specific to the ITME, particularly in T cell, NK cell, and Macrophage populations. These results suggest that aged immune cells are more susceptible to tumor suppression of cytotoxic immune cell infiltration and activity than normal tissues, which creates an unfavorable ITME in older patients in excess of normal immune decline with age and may inform the application of existing and emerging immunotherapies for this large population of patients. We additionally identify that age-related increases in tumor mutational burden are associated with decreased DNA methylation and increased expression of the immune checkpoint genes *PDL1*, *CD80*, and *LAG3* which may have implications for therapeutic application of immune checkpoint blockade in older patients.

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Early-adulthood Caloric Restriction Is Beneficial to Improve Renal Redox Status as Future Anti-Aging Strategy in Rats

Aims: Caloric restriction (CR) is an experimental approach proposed to alleviate age-related oxidative damage. In the present study, we investigated the consequences of CR on renal redox homeostasis in rats at a specific time frame in early-adulthood..

Methods: Three groups of male Sprague-Dawley rats; young control at 6-month-old, 2-year-old subjected to 40% CR between 18^{th}-24^{th} months of age, and their non-CR controls were sacrificed, and numerous redox status biomarkers including protein oxidation, glycation, lipid peroxidation, glycation end products, thiol groups, and superoxide dismutase were assayed. It was also ensured that CR rats and their non-CR corresponding rats had similar body weights at the end of the study to decrease the confounding effects of different body weights on redox homeostasis and caloric restriction.

Results: After CR, the detrimental effects of the protein oxidation, glycation, and lipid peroxidation were significantly improved in the renal tissue CR rats when compared to their non-CR control group. However, there were no significant difference in thiol fractions between younger controls and both of the elderly groups.

Conclusion: Detrimental consequences of renal senescence on redox homeostasis are significantly improved via CR especially applied in early-adulthood.

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Regular Supplementation With Resveratrol Improves Bone Mineral Density in Postmenopausal Women: A Randomised, Placebo-Controlled Trial

Resveratrol, a naturally-occurring polyphenol in red grapes and berries, can act as a phytoestrogen. It has been shown to improve both systemic and cerebral circulatory functions, possibly through activation of endothelial estrogen receptors. In vitro and in vivo studies in rodent models also indicate a bone-protective role for resveratrol, particularly in ovariectomised rat models that mimic postmenopausal osteoporosis caused by estrogen deficiency. Hypothesising a circulatory benefit of resveratrol in bone tissue, we investigated whether resveratrol supplementation could improve bone health in postmenopausal women. The Resveratrol for Healthy Ageing in Women (RESHAW) trial was a 24-month randomised, double-blind, placebo-controlled, two-period crossover intervention conducted to evaluate the effects of resveratrol (75mg twice daily) on cognition, cerebrovascular function, bone health, cardiometabolic markers and well-being in postmenopausal women. Following 12 months of supplementation with resveratrol versus placebo, there were positive effects on bone density in the lumbar spine (+0.016±0.003 g/cm^2) and neck of femur (+0.005±0.002 g/cm^2), which were accompanied by a 7.24% reduction in C-terminal telopeptide type-1 collagen levels, a bone resorption marker, compared to placebo. The increase in bone mineral density in the femoral neck resulted in an improvement in T-score (+0.070±0.018) and a reduction in the 10-year probability of major and hip fracture risk. The magnitude of improvement was higher in women with poor bone health biomarker status. Importantly, the improvement in femoral neck T-score with resveratrol correlated with improvement in perfusion. Our sub-analysis also revealed that the bone-protective benefit of resveratrol was greater in participants who supplemented with vitamin D plus calcium. Regular supplementation with 75mg of resveratrol twice daily has the potential to slow bone loss in the lumbar spine and femoral neck, common fracture sites in postmenopausal women without overt osteoporosis.

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Germline mutation rates in young adults predict longevity and reproductive lifespan

Ageing may be due to mutation accumulation across the lifespan, leading to tissue dysfunction, disease, and death. We tested whether germline autosomal mutation rates in young adults predict their remaining survival, and, for women, their reproductive lifespans. Age-adjusted mutation rates (AAMRs) in 61 women and 61 men from the Utah CEPH (Centre d'Etude du Polymorphisme Humain) families were determined. Age at death, cause of death, all-site cancer incidence, and reproductive histories were provided by the Utah Population Database, Utah Cancer Registry, and Utah Genetic Reference Project. Higher AAMRs were significantly associated with higher all-cause mortality in both sexes combined. Subjects in the top quartile of AAMRs experienced more than twice the mortality of bottom quartile subjects (hazard ratio [HR], 2.07; 95% confidence interval [CI], 1.21–3.56; p = 0.008; median survival difference = 4.7 years). Fertility analyses were restricted to women whose age at last birth (ALB) was ≥ 30 years, the age when fertility begins to decline. Women with higher AAMRs had significantly fewer live births and a younger ALB. Adult germline mutation accumulation rates are established in adolescence, and later menarche in women is associated with delayed mutation accumulation. We conclude that germline mutation rates in healthy young adults may provide a measure of both reproductive and systemic ageing. Puberty may induce the establishment of adult mutation accumulation rates, just when DNA repair systems begin their lifelong decline.

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Kinetics and Mechanisms of Mitotic Inheritance of DNA Methylation and Their Roles in Aging-Associated Methylome Deterioration

Mitotic inheritance of the DNA methylome is a challenging task for the maintenance of cell identity. Whether DNA methylation pattern in different genomic contexts can all be faithfully maintained is an open question. A replication-coupled DNA methylation maintenance model was proposed decades ago, but some observations suggest that a replication-uncoupled maintenance mechanism exists. However, the capacity and the underlying molecular events of replication-uncoupled maintenance are unclear. By measuring maintenance kinetics at the single-molecule level and assessing mutant cells with perturbation of various mechanisms, we found that the kinetics of replication-coupled maintenance are governed by the UHRF1-Ligase 1 and PCNA-DNMT1 interactions, whereas nucleosome occupancy and the interaction between UHRF1 and methylated H3K9 specifically regulate replication-uncoupled maintenance. Surprisingly, replication-uncoupled maintenance is sufficiently robust to largely restore the methylome when replication-coupled maintenance is severely impaired. However, solo-WCGW sites and other CpG sites displaying aging- and cancer-associated hypomethylation exhibit low maintenance efficiency, suggesting that although quite robust, mitotic inheritance of methylation is imperfect and that this imperfection may contribute to selective hypomethylation during aging and tumorigenesis.

Untargeted Metabolomics for Uncovering Biological Markers of Human Skeletal Muscle Ageing

Ageing compromises skeletal muscle mass and function through poorly defined molecular aetiology. Here we have used untargeted metabolomics using UHPLC-MS to profile muscle tissue from young (*n*=10, 25±4y), middle aged (*n*=18, 50±4y) and older (*n*=18, 70±3y) men and women (50:50). Random Forest was used to prioritise metabolite features most informative in stratifying older age, with potential biological context examined using the prize-collecting Steiner forest algorithm embedded in the PIUMet software, to identify metabolic pathways likely perturbed in ageing. This approach was able to filter a large dataset of several thousand metabolites down to subnetworks of age important metabolites. Identified networks included the common age-associated metabolites such as androgens, (poly)amines/amino acids and lipid metabolites, in addition to some potentially novel ageing related markers such as dihydrothymine and imidazolone-5-proprionic acid. The present study reveals that this approach is a potentially useful tool to identify processes underlying human tissue ageing, and could therefore be utilised in future studies to investigate the links between age predictive metabolites and common biomarkers linked to health and disease across age.

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Differential role of cytosolic Hsp70s in longevity assurance and protein quality control

70 kDa heat shock proteins (Hsp70) are essential chaperones of the protein quality control network; vital for cellular fitness and longevity. The four cytosolic Hsp70's in yeast, Ssa1-4, are thought to be functionally redundant but the absence of Ssa1 and Ssa2 causes a severe reduction in cellular reproduction and accelerates replicative aging. In our efforts to identify which Hsp70 activities are most important for longevity assurance, we systematically investigated the capacity of Ssa4 to carry out the different activities performed by Ssa1/2 by overproducing Ssa4 in cells lacking these Hsp70 chaperones. We found that Ssa4, when overproduced in cells lacking Ssa1/2, rescued growth, mitigated aggregate formation, restored spatial deposition of aggregates into protein inclusions, and promoted protein degradation. In contrast, Ssa4 overproduction in the Hsp70 deficient cells failed to restore the recruitment of the disaggregase Hsp104 to misfolded/aggregated proteins, to fully restore clearance of protein aggregates, and to bring back the formation of the nucleolus-associated aggregation compartment. Exchanging the nucleotide-binding domain of Ssa4 with that of Ssa1 suppressed this 'defect' of Ssa4. Interestingly, Ssa4 overproduction extended the short lifespan of *ssa1*Δ *ssa2*Δ mutant cells to a lifespan comparable to, or even longer than, wild type cells, demonstrating that Hsp104-dependent aggregate clearance is not a prerequisite for longevity assurance in yeast.

C. elegans aging research

MicroPubl Biol. 2020; 2020: 10.17912/micropub.biology.000257.
Published online 2020 May 27. doi: 10.17912/micropub.biology.000257
PMCID: PMC7253371
PMID: 32550518

Caenorhabditis Intervention Testing Program: the farnesoid X receptor agonist obeticholic acid does not robustly extend lifespan in nematodes

Our results indicate that obeticholic acid does not have a consistent beneficial effect on lifespan in any of the *C. elegans* or *C. briggsae* strains tested at the concentrations used. Although we did see some significant differences from the control for some of the concentrations in the *C. tropicalis* strains, overall the difference was not robust. We actually saw a significant decrease in lifespan in *C. tropicalis* JU1630, a weakly significant increase in *C. tropicalis* QG834 at some concentrations, and a relatively significant increase in *C. tropicalis* JU1373, but with only a 5.7-7.9% change in mean survival from the control (Fig. 1). In summary, our results do not indicate a robust effect of obeticholic acid on *Caenorhabditis* lifespan. This conclusion is based upon two biological replicates at each concentration performed in one lab, resulting in an average of 104 individuals measured per strain and concentration, and should be considered preliminary. The effect on lifespan in this study may pertain to a lack of physiological relevance of obeticholic acid to *Caenorhabditis*. Obeticholic acid was of interest to the CITP because of its effect on the mammalian NR FXR. Although DAF-12 has been identified as a potential *Caenorhabditis* homolog of FXR and other bile acids have been shown to bind with DAF-12 (Zhi *et al.* 2011), it is possible that obeticholic acid was not able to bind with high affinity to the receptor, therefore eliciting little to no effect on lifespan. Alternatively, obeticholic acid may be rapidly metabolized in *Caenorhabditis*.

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A transcriptome based aging clock near the theoretical limit of accuracy

David H. Meyer, Björn Schumacher

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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IMPACT OF PHENOLIC ACIDS ON THE ENERGY METABOLISM AND LONGEVITY IN *C. ELEGANS*

Introduction Aging represents one of the major risk factors for metabolic diseases, such as diabetes and obesity, or neurodegeneration. Polyphenols and its metabolites, especially simple phenolic acids, have gained more and more attention as a preventive strategy for age-related, non-communicable diseases, due to their hormetic potential. Using the nematode *Caenorhabditis elegans* (*C. elegans*) we investigate the effect of protocatechuic, gallic and vanillic acid to improve mitochondrial function and health associated parameters as a preventive measure.

Methods Lifespan, heat-stress resistance and chemotaxis of *C. elegans* strain PX627, as a specific model for aging, were assessed in 2-day and 10-day old nematodes. Mitochondrial membrane potential ($\Delta\Psi m$) and ATP generation of young and aged nematodes were measured. mRNA expression levels of longevity and energy metabolism-related genes were determined using qRT-PCR.

Results All phenolic acids were able to significantly increase the nematodes lifespan, heat-stress resistance and chemotaxis at micromolar concentrations. While $\Delta\Psi m$ was only affected by age, vanillic acid significantly decreased ATP concentrations in aged nematodes. Genetic analysis revealed increased glycolytic activity mediated through vanillic acid, suggesting improved thermogenesis.

Conclusion While life- and health-span parameters are positively affected by the investigated phenolic acids, the concentrations applied were unable to impact mitochondrial performance, suggesting hormesis. In contrast to the other phenolic acids, vanillic acid showed potential in regulating glucose homeostasis, making it a prime candidate for future diabetes and obesity focused approaches.

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Composition of *Caenorhabditis elegans* extracellular vesicles suggests roles in metabolism, immunity, and aging

Joshua C. Russell ✉, Taek-Kyun Kim, Ayush Noori, Gennifer E. Merrihew, Julia E. Robbins, Alexandra Golubeva, Kai Wang, Michael J. MacCoss & Matt Kaeberlein ✉

The nematode *Caenorhabditis elegans* has been instrumental in the identification of evolutionarily conserved mechanisms of aging. *C. elegans* also has recently been found to have evolutionarily conserved extracellular vesicle (EV) signaling pathways. We have been developing tools that allow for the detailed study of EV biology in *C. elegans*. Here we apply our recently published method for high specificity purification of EVs from *C. elegans* to carry out target-independent proteomic and RNA analysis of nematode EVs. We identify diverse coding and non-coding RNA and protein cargo types commonly found in human EVs. The EV cargo spectrum is distinct from whole worms, suggesting that protein and RNA cargos are actively recruited to EVs. Gene ontology analysis revealed *C. elegans* EVs are enriched for extracellular-associated and signaling proteins, and network analysis indicates enrichment for metabolic, immune, and basement membrane associated proteins. Tissue enrichment and gene expression analysis suggests the secreted EV proteins are likely to be derived from intestine, muscle, and excretory tissue. An unbiased comparison of the EV proteins with a large database of *C. elegans* genome-wide microarray data showed significant overlap with gene sets that are associated with aging and immunity. Taken together our data suggest *C. elegans* could be a promising in vivo model for studying the genetics and physiology of EVs in a variety of contexts including aging, metabolism, and immune response.

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Lifespan and Healthspan Benefits of Exogenous H_2S in *C. elegans* Are Independent From Effects Downstream of *eat-2* Mutation

Li Theng Ng [1 2 3], Li Fang Ng [1], Richard Ming Yi Tang [4 3 5], Diogo Barardo [1 4], Barry Halliwell [4 3], Philip Keith Moore [2 3], Jan Gruber [1 4]

Caloric restriction (CR) is one of the most effective interventions to prolong lifespan and promote health. Recently, it has been suggested that hydrogen sulfide (H_2S) may play a pivotal role in mediating some of these CR-associated benefits. While toxic at high concentrations, H_2S at lower concentrations can be biologically advantageous. H_2S levels can be artificially elevated *via* H_2S-releasing donor drugs. In this study, we explored the function of a novel, slow-releasing H_2S donor drug (FW1256) and used it as a tool to investigate H_2S in the context of CR and as a potential CR mimetic. We show that exposure to FW1256 extends lifespan and promotes health in *Caenorhabditis elegans* (*C. elegans*) more robustly than some previous H_2S-releasing compounds, including GYY4137. We looked at the extent to which FW1256 reproduces CR-associated physiological effects in normal-feeding *C. elegans*. We found that FW1256 promoted healthy longevity to a similar degree as CR but with fewer fitness costs. In contrast to CR, FW1256 actually enhanced overall reproductive capacity and did not reduce adult body length. FW1256 further extended the lifespan of already long-lived *eat-2* mutants without further detriments in developmental timing or fertility, but these lifespan and healthspan benefits required H_2S exposure to begin early in development. Taken together, these observations suggest that FW1256 delivers exogenous H_2S efficiently and supports a role for H_2S in mediating longevity benefits of CR. Delivery of H_2S *via* FW1256, however, does not mimic CR perfectly, suggesting that the role of H_2S in CR-associated longevity is likely more complex than previously described.

Water Is a Biomarker of Changes in the Cellular Environment in Live Animals

Pratibha Siwach [1], Evgeniya Levy [2], Leonid Livshits [3], Yuri Feldman [2], Daniel Kaganovich [4 5]

The biological processes that are associated with the physiological fitness state of a cell comprise a diverse set of molecular events. Reactive oxygen species (ROS), mitochondrial dysfunction, telomere shortening, genomic instability, epigenetic changes, protein aggregation, and down-regulation of quality control mechanisms are all hallmarks of cellular decline. Stress-related and decline-related changes can be assayed, but usually through means that are highly disruptive to living cells and tissues. Biomarkers for organismal decline and aging are urgently needed for diagnostic and drug development. Our goal in this study is to provide a proof-of-concept for a non-invasive assay of global molecular events in the cytoplasm of living animals. We show that Microwave Dielectric Spectroscopy (MDS) can be used to determine the hydration state of the intracellular environment in live C. elegans worms. MDS spectra were correlative with altered states in the cellular protein folding environment known to be associated with previously described mutations in the C. elegans lifespan and stress-response pathways.

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Sub-nanowatt resolution direct calorimetry for probing real-time metabolic activity of individual *C. elegans* worms

Calorimetry has been widely used in metabolic studies, but direct measurements from individual small biological model organisms such as *C. elegans* or isolated single cells have been limited by poor sensitivity of existing techniques and difficulties in resolving very small heat outputs. Here, by careful thermal engineering, we developed a robust, highly sensitive and bio-compatible calorimetric platform that features a resolution of ~270 pW—more than a 500-fold improvement over the most sensitive calorimeter previously used for measuring the metabolic heat output of *C. elegans*. Using this calorimeter, we demonstrate time-resolved metabolic measurements of single *C. elegans* worms from larval to adult stages. Further, we show that the metabolic output is significantly lower in long-lived *C. elegans daf-2* mutants. These demonstrations clearly highlight the broad potential of this tool for studying the role of metabolism in disease, development and aging of small model organisms and single cells.

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Transgenerational fitness effects of lifespan extension by dietary restriction in *Caenorhabditis elegans*

Edward R. Ivimey-Cook, Kris Sales, Hanne Carlsson, Simone Immler, Tracey Chapman, Alexei A. Maklakov

Dietary restriction increases lifespan in a broad variety of organisms and improves health in humans. However, long-term transgenerational consequences of dietary interventions are poorly understood. Here we investigated the effect of dietary restriction by temporary fasting (TF) on mortality risk, age-specific reproduction and fitness across three generations of descendants in *C. elegans*. We show that while TF robustly reduces mortality risk and improves late-life reproduction in the parental generation (P_0), it has a wide range of both positive and deleterious effects on future generations (F_1-F_3). Remarkably, great-grandparental exposure to TF in early-life reduces fitness and increases mortality risk of F_3 descendants to such an extent that TF no longer promotes a lifespan extension. These findings reveal that transgenerational trade-offs accompany the instant benefits of dietary restriction underscoring the need to consider fitness of future generations in pursuit of healthy ageing.

Lysosome Activity Is Modulated by Multiple Longevity Pathways and Is Important for Lifespan Extension in *C. elegans*

Lysosomes play important roles in cellular degradation to maintain cell homeostasis. In order to understand whether and how lysosomes alter with age and contribute to lifespan regulation, we characterized multiple properties of lysosomes during the aging process in *C. elegans*. We uncovered age-dependent alterations in lysosomal morphology, motility, acidity and degradation activity, all of which indicate a decline in lysosome function with age. The age-associated lysosomal changes are suppressed in the long-lived mutants *daf-2*, *eat-2* and *isp-1*, which extend lifespan by inhibiting insulin/IGF-1 signaling, reducing food intake and impairing mitochondrial function, respectively. We found that 43 lysosome genes exhibit reduced expression with age, including genes encoding subunits of the proton pump V-ATPase and cathepsin proteases. The expression of lysosome genes is upregulated in the long-lived mutants, and this upregulation requires the functions of DAF-16/FOXO and SKN-1/NRF2 transcription factors. Impairing lysosome function affects clearance of aggregate-prone proteins and disrupts lifespan extension in *daf-2*, *eat-2* and *isp-1* worms. Our data indicate that lysosome function is modulated by multiple longevity pathways and is important for lifespan extension.

Repetitive Elements as a Transcriptomic Marker of Aging: Evidence in Multiple Datasets and Models

Transcriptomic markers of aging can be useful for studying age-related processes and diseases. However, noncoding repetitive element (RE) transcripts, which may play an important role in aging, are commonly overlooked in transcriptome studies-and their potential as a transcriptomic marker of aging has not been evaluated. Here, we used multiple RNA-seq datasets generated from human samples and Caenorhabditis elegans and found that most RE transcripts (a) accumulate progressively with aging; (b) can be used to accurately predict age; and (c) may be a good marker of biological age. The strong RE/aging correlations we observed are consistent with growing evidence that RE transcripts contribute directly to aging and disease.

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Induction of RNA interference by *C. elegans* mitochondrial dysfunction via the DRH-1/RIG-I homologue RNA helicase and the EOL-1/RNA decapping enzyme

Kai Mao, Peter Breen, Gary Ruvkun

RNA interference (RNAi) is an antiviral pathway common to many eukaryotes that detects and cleaves foreign nucleic acids. In mammals, mitochondrially localized proteins such as MAVS, RIG-I, and MDA5 mediate antiviral responses. Here, we report that mitochondrial dysfunction in *Caenorhabditis elegans* activates RNAi-directed silencing via induction of a pathway homologous to the mammalian RIG-I helicase viral response pathway. The induction of RNAi also requires the conserved RNA decapping enzyme EOL-1/DXO. The transcriptional induction of *eol-1* requires DRH-1 as well as the mitochondrial unfolded protein response (UPR^{mt}). Upon mitochondrial dysfunction, EOL-1 is concentrated into foci that depend on the transcription of mitochondrial RNAs that may form dsRNA, as has been observed in mammalian antiviral responses. The enhanced RNAi triggered by mitochondrial dysfunction contributes to the increase in longevity that is induced by mitochondrial dysfunction.

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NFYB-1 regulates mitochondrial function and longevity via lysosomal prosaposin

Mitochondria are multidimensional organelles whose activities are essential to cellular vitality and organismal longevity, yet underlying regulatory mechanisms spanning these different levels of organization remain elusive[1,2,3,4,5]. Here we show that *Caenorhabditis elegans* nuclear transcription factor Y, beta subunit (NFYB-1), a subunit of the NF-Y transcriptional complex[6,7,8], is a crucial regulator of mitochondrial function. Identified in RNA interference (RNAi) screens, NFYB-1 loss leads to perturbed mitochondrial gene expression, reduced oxygen consumption, mitochondrial fragmentation, disruption of mitochondrial stress pathways, decreased mitochondrial cardiolipin levels and abolition of organismal longevity triggered by mitochondrial impairment. Multi-omics analysis reveals that NFYB-1 is a potent repressor of lysosomal prosaposin, a regulator of glycosphingolipid metabolism. Limiting prosaposin expression unexpectedly restores cardiolipin production, mitochondrial function and longevity in the *nfyb-1* background. Similarly, cardiolipin supplementation rescues *nfyb-1* phenotypes. These findings suggest that the NFYB-1–prosaposin axis coordinates lysosomal to mitochondria signalling via lipid pools to enhance cellular mitochondrial function and organismal health.

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Males deploy multifaceted strategies and hijack longevity pathways to induce premature demise of the opposite sex

Interactions between the sexes negatively impact health in many species, including mammals[1-9]. In mice, sexual interactions induce weight gain and shorten lifespan in females, independent of fertilization[6,9]. In *Caenorhabditis*, males shorten the lifespan of the opposite sex (females or hermaphrodites)[1-3,8]. However, the mechanisms underlying the negative influence of males on lifespan – and their overlap with known longevity pathways – are still largely unknown. Here, we use transcriptomic profiling and targeted screens to systematically uncover new conserved genes involved in male-induced demise. Interestingly, deficiency of these genes individually, and especially in combination, induces strong protection, highlighting the benefit of combining interventions to extend lifespan. Some genes (e.g. *acbp-3, col-43*) only extend hermaphrodite lifespan when knocked-down in the presence of males, suggesting specific protective mechanisms against male-induced demise. However, we also uncover two previously unknown longevity genes (*sri-40* and *delm-2*) that, when knocked-down, extend hermaphrodite lifespan both with and without males, which points to new broad mechanisms of resistance. In sharp contrast, many classical long-lived mutants are actually short-lived in the presence of males, suggesting that males hijack and suppress known longevity pathways. This systematic analysis reveals striking differences in longevity in single sex versus mixed sex environments and uncovers the elaborate network of functional regulation elicited by sexual interactions, which could extend to other species.

REVIEWS/COMMENTS/ METHODS/EDITORIALS

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Treating age-related multimorbidity: the drug discovery challenge

Christos Ermogenous [1], Charlotte Green [2], Thomas Jackson [1], Michael Ferguson [2], Janet M. Lord [1, 3]

Patients with multimorbidities have shorter life expectancy and their clinical management is more complex and expensive for healthcare systems currently focused on treating single diseases. Given that age is the major risk factor for multimorbidity, the challenge of treating these patients will only increase in coming years. Here, we review the case for targeting the core processes that drive the ageing phenotype as a novel pharmaceutical approach to multimorbidity. There is growing evidence that targeting ageing mechanisms can reduce or delay age-related diseases in animal models, and the first reports of clinical trials are now appearing. Although these trials currently focus on repurposed drugs, we propose several novel targets that would more specifically target ageing processes and thereby reduce multimorbidity and polypharmacy in future generations.

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Classical and Nonclassical Intercellular Communication in Senescence and Ageing

Juan Antonio Fafián-Labora [1], Ana O'Loghlen [2]

Affiliations + expand

PMID: 32505550 DOI: 10.1016/j.tcb.2020.05.003

Abstract

Intercellular communication refers to the different ways through which cells communicate with each other and transfer a variety of messages. These communication methods involve a number of different processes that occur individually or simultaneously, which change depending on the physiological or pathological context. The best characterized means of intercellular communication is the release of soluble factors that affect the function of neighboring cells. However, there are many other ways by which cells can communicate with each other. Here, we review the different means of intercellular communication including soluble factors in the context of senescence, ageing, and age-related diseases.

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Old and new models for the study of human ageing

Anne Brunet

Nature Reviews Molecular Cell Biology (2020) | Cite this article

Human ageing is associated with high susceptibility to disease. Some aspects of ageing can be studied directly in humans and have revealed that ageing is influenced by many factors, including genetics, lifestyle, sex and socio-economic status. But identifying the factors that cause and modulate the ageing process often requires experimental interventions and modelling that can only be performed in model systems.

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Compounds That Extend Longevity Are Protective in Neurodegenerative Diseases and Provide a Novel Treatment Strategy for These Devastating Disorders

While aging is the greatest risk factor for the development of neurodegenerative disease, the role of aging in these diseases is poorly understood. In the inherited forms of these diseases, the disease-causing mutation is present from birth but symptoms appear decades later. This indicates that these mutations are well tolerated in younger individuals but not in older adults. Based on this observation, we hypothesized that changes taking place during normal aging make the cells in the brain (and elsewhere) susceptible to the disease-causing mutations. If so, then delaying some of these age-related changes may be beneficial in the treatment of neurodegenerative disease. In this review, we examine the effects of five compounds that have been shown to extend longevity (metformin, rapamycin, resveratrol, N-acetyl-L-cysteine, curcumin) in four of the most common neurodegenerative diseases (Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis). While not all investigations observe a beneficial effect of these compounds, there are multiple studies that show a protective effect of each of these lifespan-extending compounds in animal models of neurodegenerative disease. Combined with genetic studies, this suggests the possibility that targeting the aging process may be an effective strategy to treat neurodegenerative disease.

Biophysical Studies of Protein Misfolding and Aggregation in *in vivo* Models of Alzheimer's and Parkinson's Diseases

Tessa Sinnige [1], Karen Stroobants [1], Christopher M Dobson [1], Michele Vendruscolo [1]

Neurodegenerative disorders, including Alzheimer's (AD) and Parkinson's diseases (PD), are characterised by the formation of aberrant assemblies of misfolded proteins. The discovery of disease-modifying drugs for these disorders is challenging, in part because we still have a limited understanding of their molecular origins. In this review, we discuss how biophysical approaches can help explain the formation of the aberrant conformational states of proteins whose neurotoxic effects underlie these diseases. We discuss in particular models based on the transgenic expression of amyloid-β (Aβ) and tau in AD, and α-synuclein in PD. Because biophysical methods have enabled an accurate quantification and a detailed understanding of the molecular mechanisms underlying protein misfolding and aggregation in vitro, we expect that the further development of these methods to probe directly the corresponding mechanisms in vivo will open effective routes for diagnostic and therapeutic interventions.

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Deep learning for biological age estimation

Syed Ashiqur Rahman ✉, Peter Giacobbi, Lee Pyles, Charles Mullett, Gianfranco Doretto, Donald A Adjeroh

Modern machine learning techniques (such as deep learning) offer immense opportunities in the field of human biological aging research. Aging is a complex process, experienced by all living organisms. While traditional machine learning and data mining approaches are still popular in aging research, they typically need feature engineering or feature extraction for robust performance. Explicit feature engineering represents a major challenge, as it requires significant domain knowledge. The latest advances in deep learning provide a paradigm shift in eliciting meaningful knowledge from complex data without performing explicit feature engineering. In this article, we review the recent literature on applying deep learning in biological age estimation. We consider the current data modalities that have been used to study aging and the deep learning architectures that have been applied. We identify four broad classes of measures to quantify the performance of algorithms for biological age estimation and based on these evaluate the current approaches. The paper concludes with a brief discussion on possible future directions in biological aging research using deep learning. This study has significant potentials for improving our understanding of the health status of individuals, for instance, based on their physical activities, blood samples and body shapes. Thus, the results of the study could have implications in different health care settings, from palliative care to public health.

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Role of immune cells in the removal of deleterious senescent cells

Abhijit Kale, Amit Sharma, Alexandra Stolzing, Pierre-Yves Desprez & Judith Campisi

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.

Lymphatic Capillaries in Aging

Bojana Jakic [1] [2], Dontscho Kerjaschki [3], Georg Wick [4]

The lymphatic system is responsible for fluid drainage from almost every organ in the body. It sustains tissue homeostasis and is also a central part of the immune system. With the discovery of cell-specific markers and transgenic mouse models, it has become possible to gain some insight into the developmental and functional roles of lymphatic endothelial cells (LECs). Only recently, a more direct regulatory role has been assigned to LECs in their functions in immunity responses and chronic diseases. Here, we discuss the changes occurring in aged lymphatic system and the role of lymphatic capillaries in some age-related diseases and experimental animal models.

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LSEC Model of Aging

Laurent Grosse [1], Dmitry V Bulavin [1]

Affiliations + expand

PMID: 32535553 DOI: 10.18632/aging.103492

Free article

Abstract

Data obtained from genetically modified mouse models suggest a detrimental role for $p16^{High}$ senescent cells in physiological aging and age-related pathologies. Our recent analysis of aging mice revealed a continuous and noticeable accumulation of liver sinusoid endothelial cells (LSECs) expressing numerous senescence markers, including p16. At early stage, senescent LSECs show an enhanced ability to clear macromolecular waste and toxins including oxidized LDL (oxLDL). Later in life, however, the efficiency of this important detoxifying function rapidly declines potentially due to increased endothelial thickness and senescence-induced silencing of scavenger receptors and endocytosis genes. This inability to detoxify toxins and macromolecular waste, which can be further exacerbated by increased intestinal leakiness with age, might be an important contributing factor to animal death. Here, we propose how LSEC senescence could serve as an endogenous clock that ultimately controls longevity and outline some of the possible approaches to extend the lifespan.

Nuclear Periphery Takes Center Stage: The Role of Nuclear Pore Complexes in Cell Identity and Aging

Ukrae H Cho [1], Martin W Hetzer [2]

In recent years, the nuclear pore complex (NPC) has emerged as a key player in genome regulation and cellular homeostasis. New discoveries have revealed that the NPC has multiple cellular functions besides mediating the molecular exchange between the nucleus and the cytoplasm. In this review, we discuss non-transport aspects of the NPC focusing on the NPC-genome interaction, the extreme longevity of the NPC proteins, and NPC dysfunction in age-related diseases. The examples summarized herein demonstrate that the NPC, which first evolved to enable the biochemical communication between the nucleus and the cytoplasm, now doubles as the gatekeeper of cellular identity and aging.

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Calorie Restriction and Aging in Humans

Emily W Flanagan [1], Jasper Most [2], Jacob T Mey [1], Leanne M Redman [1]

Affiliations + expand

PMID: 32559388 DOI: 10.1146/annurev-nutr-122319-034601

Abstract

Calorie restriction (CR), the reduction of dietary intake below energy requirements while maintaining optimal nutrition, is the only known nutritional intervention with the potential to attenuate aging. Evidence from observational, preclinical, and clinical trials suggests the ability to increase life span by 1-5 years with an improvement in health span and quality of life lived. CR moderates intrinsic processes of aging through cellular and metabolic adaptations and reducing risk for the development of many cardiometabolic diseases. Yet, implementation of CR may require unique considerations for the elderly and other specific populations. The objectives of this review are to summarize the evidence for CR to modify primary and secondary aging; present caveats for implementation in special populations; describe newer, alternative approaches that have comparative effectiveness and fewer deleterious effects; and provide thoughts on the future of this important field of study. Please see http://www.annualreviews.org/page/journal/pubdates for expected final online publication date for the *Annual Review of Nutrition*, Volume 40. 2020.

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Matrix Metalloproteinases as New Targets in Alzheimer's Disease: Opportunities and Challenges

Pauline Zipfel, Christophe Rochais, Kévin Baranger, Santiago Rivera, and Patrick Dallemagne*

Although matrix metalloproteinases (MMPs) are implicated in the regulation of numerous physiological processes, evidence of their pathological roles have also been obtained in the last decades, making MMPs attractive therapeutic targets for several diseases. Recent discoveries of their involvement in central nervous system (CNS) disorders, and in particular in Alzheimer's disease (AD), have paved the way to consider MMP modulators as promising therapeutic strategies. Over the past few decades, diverse approaches have been undertaken in the design of therapeutic agents targeting MMPs for various purposes, leading, more recently, to encouraging developments. In this article, we will present recent examples of inhibitors ranging from small molecules and peptidomimetics to biologics. We will also discuss the scientific knowledge that has led to the development of emerging tools and techniques to overcome the challenges of selective MMP inhibition.

Stochastic non-enzymatic modification of long-lived macromolecules - A missing hallmark of aging

Damage accumulation in long-living macromolecules (especially extracellular matrix (ECM) proteins, nuclear pore complex (NPC) proteins, and histones) is a missing hallmark of aging. Stochastic non-enzymatic modifications of ECM trigger cellular senescence as well as many other hallmarks of aging affect organ barriers integrity and drive tissue fibrosis. The importance of it for aging makes it a key target for interventions. The most promising of them can be AGE inhibitors (chelators, O-acetyl group or transglycating activity compounds, amadorins and amadoriases), glucosepane breakers, stimulators of elastogenesis, and RAGE antagonists.

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The Aging Transcriptome: Read Between the Lines

Anabel Perez-Gomez [1], Joel N Buxbaum [2], Michael Petrascheck [3]

Affiliations + expand

PMID: 32563038 DOI: 10.1016/j.conb.2020.05.001

Abstract

The increasing sophistication of gene expression technologies has given rise to the idea that aging could be understood by analyzing transcriptomes. Mapping trajectories of gene expression changes in aging organisms, across different tissues and brain regions has provided insights on how biological functions change with age. However, recent publications suggest that transcriptional regulation itself deteriorates with age. Loss of transcriptional regulation will lead to non-regulated gene expression changes, but current analysis strategies were not designed to disentangle mixtures of regulated and non-regulated changes. Disentangling transcriptional data to distinguish adaptive, regulatory changes, from those that are the consequence of the age-associated deterioration is likely to create an analytical challenge but promises to unlock yet poorly understood aspects of many age-associated transcriptomes.

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The Circuitry Between Ribosome Biogenesis and Translation in Stem Cell Function and Ageing

Ribosome biogenesis takes place mainly in the nucleolus, a nuclear, non-membrane bound organelle forming around the gene arrays encoding ribosomal RNA (rRNA). Nucleolar activity comprises synthesis, processing and maturation of rRNAs, followed by their assembly with ribosomal proteins into pre-ribosomal particles. The final formation of translation-competent ribosomes in the cytoplasm is the prerequisite for protein synthesis, which is the most energy-consuming cellular process. In adult stem cells, ribosome biogenesis and protein synthesis determine the switch between the quiescent and the activated state, but also decide whether activated stem cells self-renew or differentiate. Given this major impact on cellular function, it seems likely that perturbations of the circuitry between nucleolar activity and translation lead to ageing-related stem cell deterioration. This review provides an overview of how ribosome biogenesis and translation govern stem cell function and discusses the resultant implication in stem cell ageing.

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Metabolic Communication and Healthy Aging: Where Should We Focus Our Energy?

Hannah J Smith [1], Arpit Sharma [1], William B Mair [2]

Aging is associated with a loss of metabolic homeostasis and plasticity, which is causally linked to multiple age-onset pathologies. The majority of the interventions-genetic, dietary, and pharmacological-that have been found to slow aging and protect against age-related disease in various organisms do so by targeting central metabolic pathways. However, targeting metabolic pathways chronically and ubiquitously makes it difficult to define the downstream effects responsible for lifespan extension and often results in negative effects on growth and health, limiting therapeutic potential. Insight into how metabolic signals are relayed between tissues, cells, and organelles opens up new avenues to target metabolic regulators locally rather than globally for healthy aging. In this review, we discuss the pro-longevity effects of targeting metabolic pathways in specific tissues and how these interventions communicate with distal cells to modulate aging. These studies may be crucial in designing interventions that promote longevity without negative health consequences.

Saturated Fats and Health: A Reassessment and Proposal for Food-based Recommendations: JACC State-of -the-Art Review

The recommendation to limit dietary saturated fatty acid (SFA) intake has persisted despite mounting evidence to the contrary. Most recent meta-analyses of randomized trials and observational studies found no beneficial effects of reducing SFA intake on cardiovascular disease (CVD) and total mortality, and instead found protective effects against stroke. Although SFAs increase low-density lipoprotein (LDL)-cholesterol, in most individuals, this is not due to increasing levels of small, dense LDL particles, but rather larger LDL which are much less strongly related to CVD risk. It is also apparent that the health effects of foods cannot be predicted by their content in any nutrient group, without considering the overall macronutrient distribution. Whole-fat dairy, unprocessed meat, eggs and dark chocolate are SFA-rich foods with a complex matrix that are not associated with increased risk of CVD. The totality of available evidence does not support further limiting the intake of such foods.

OTHER RESEARCH & REVIEWS

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The mutational constraint spectrum quantified from variation in 141,456 humans

Genetic variants that inactivate protein-coding genes are a powerful source of information about the phenotypic consequences of gene disruption: genes that are crucial for the function of an organism will be depleted of such variants in natural populations, whereas non-essential genes will tolerate their accumulation. However, predicted loss-of-function variants are enriched for annotation errors, and tend to be found at extremely low frequencies, so their analysis requires careful variant annotation and very large sample sizes[1]. Here we describe the aggregation of 125,748 exomes and 15,708 genomes from human sequencing studies into the Genome Aggregation Database (gnomAD). We identify 443,769 high-confidence predicted loss-of-function variants in this cohort after filtering for artefacts caused by sequencing and annotation errors. Using an improved model of human mutation rates, we classify human protein-coding genes along a spectrum that represents tolerance to inactivation, validate this classification using data from model organisms and engineered human cells, and show that it can be used to improve the power of gene discovery for both common and rare diseases.

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Fasting mimicking diet as an adjunct to neoadjuvant chemotherapy for breast cancer in the multicentre randomized phase 2 DIRECT trial

Short-term fasting protects tumor-bearing mice against the toxic effects of chemotherapy while enhancing therapeutic efficacy. We randomized 131 patients with HER2-negative stage II/III breast cancer, without diabetes and a BMI over 18 kg m^{-2}, to receive either a fasting mimicking diet (FMD) or their regular diet for 3 days prior to and during neoadjuvant chemotherapy. Here we show that there was no difference in toxicity between both groups, despite the fact that dexamethasone was omitted in the FMD group. A radiologically complete or partial response occurs more often in patients using the FMD (OR 3.168, P = 0.039). Moreover, per-protocol analysis reveals that the Miller&Payne 4/5 pathological response, indicating 90–100% tumor-cell loss, is more likely to occur in patients using the FMD (OR 4.109, P = 0.016). Also, the FMD significantly curtails chemotherapy-induced DNA damage in T-lymphocytes. These positive findings encourage further exploration of the benefits of fasting/FMD in cancer therapy. Trial number: NCT02126449.

Protein Arginine Deiminase 4 Antagonizes Methylglyoxal-Induced Histone Glycation

Protein arginine deiminase 4 (PAD4) facilitates the post-translational citrullination of the core histones H3 and H4. While the precise epigenetic function of this modification has not been resolved, it has been shown to associate with general chromatin decompaction and compete with arginine methylation. Recently, we found that histones are subjected to methylglyoxal (MGO)-induced glycation on nucleophilic side chains, particularly arginines, under metabolic stress conditions. These non-enzymatic adducts change chromatin architecture and the epigenetic landscape by competing with enzymatic modifications, as well as changing the overall biophysical properties of the fiber. Here, we report that PAD4 antagonizes histone MGO-glycation by protecting the reactive arginine sites, as well as by converting already-glycated arginine residues into citrulline. Moreover, we show that similar to the deglycase DJ-1, PAD4 is overexpressed and histone citrullination is upregulated in breast cancer tumors, suggesting an additional mechanistic link to PAD4's oncogenic properties.

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Zeb2 drives invasive and microbiota-dependent colon carcinoma

Colorectal cancer (CRC) is highly prevalent in Western society, and increasing evidence indicates strong contributions of environmental factors and the intestinal microbiota to CRC initiation, progression and even metastasis. We have identified a synergistic inflammatory tumor-promoting mechanism through which the resident intestinal microbiota boosts invasive CRC development in an epithelial-to-mesenchymal transition-prone tissue environment. Intestinal epithelial cell (IEC)-specific transgenic expression of the epithelial-to-mesenchymal transition regulator Zeb2 in mice ($Zeb2^{IEC\text{-}Tg/+}$) leads to increased intestinal permeability, myeloid cell-driven inflammation and spontaneous invasive CRC development. $Zeb2^{IEC\text{-}Tg/+}$ mice develop a dysplastic colonic epithelium, which progresses to severely inflamed neoplastic lesions while the small intestinal epithelium remains normal. $Zeb2^{IEC\text{-}Tg/+}$ mice are characterized by intestinal dysbiosis, and microbiota depletion with broad-spectrum antibiotics or germ-free rederivation completely prevents cancer development. $Zeb2^{IEC\text{-}Tg/+}$ mice represent the first mouse model of spontaneous microbiota-dependent invasive CRC and will help us to better understand host–microbiome interactions driving CRC development in humans.