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6th of September 2020
Sven Bulterijs

Business/Conferences/ General news

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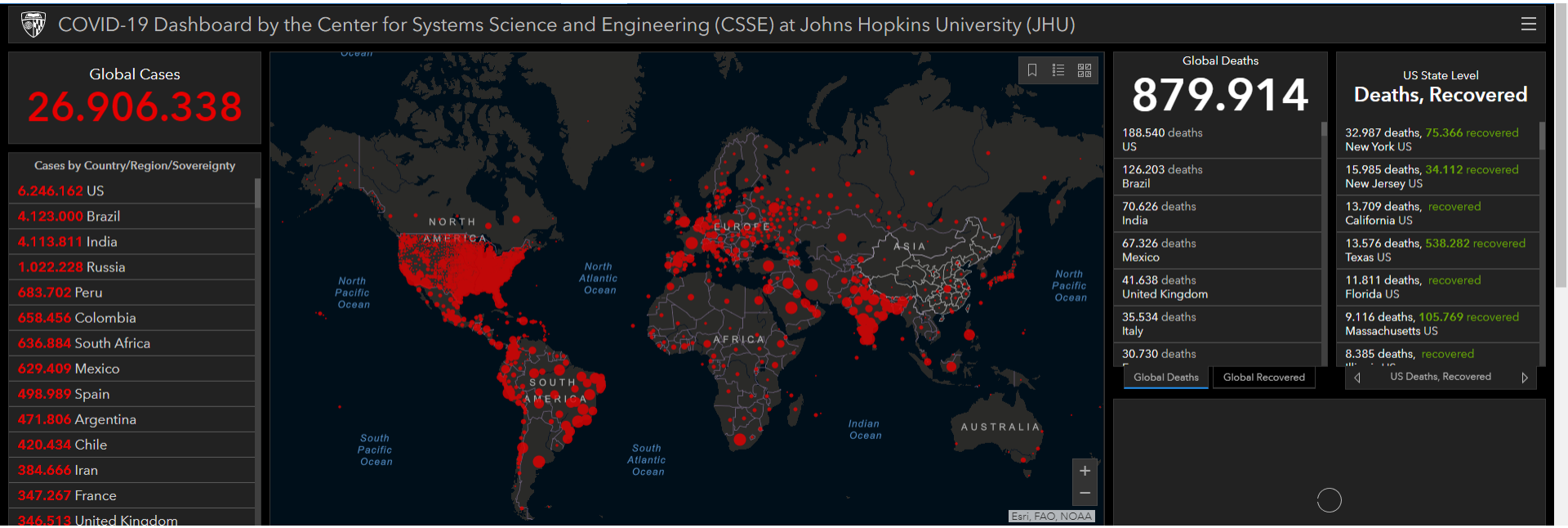

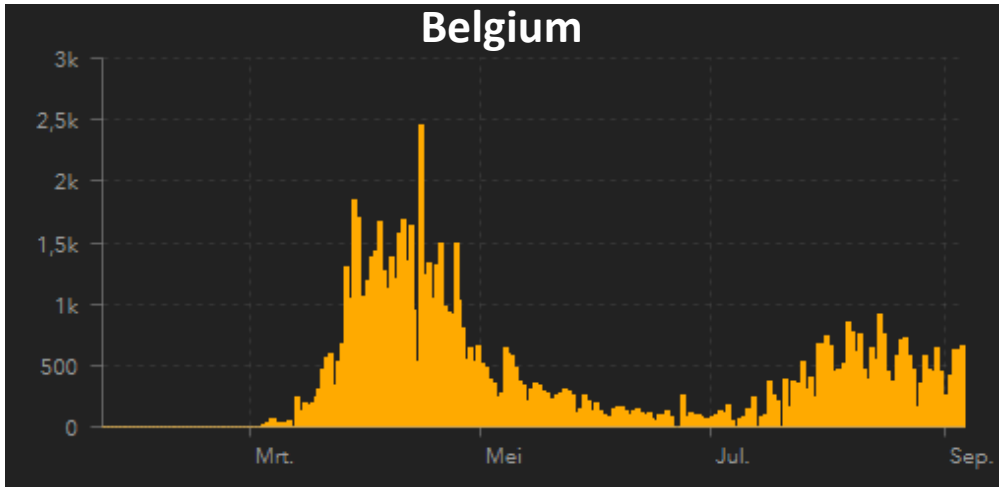

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Masks Do More Than Protect Others During COVID-19: Reducing the Inoculum of SARS-CoV-2 to Protect the Wearer

Although the benefit of population-level public facial masking to protect others during the COVID-19 pandemic has received a great deal of attention, we discuss for one of the first times the hypothesis that universal masking reduces the "inoculum" or dose of the virus for the mask-wearer, leading to more mild and asymptomatic infection manifestations. Masks, depending on type, filter out the majority of viral particles, but not all. We first discuss the near-century-old literature around the viral inoculum and severity of disease (conceptualized as the LD50 or lethal dose of the virus). We include examples of rising rates of asymptomatic infection with population-level masking, including in closed settings (e.g., cruise ships) with and without universal masking. Asymptomatic infections may be harmful for spread but could actually be beneficial if they lead to higher rates of exposure. Exposing society to SARS-CoV-2 without the unacceptable consequences of severe illness with public masking could lead to greater community-level immunity and slower spread as we await a vaccine. This theory of viral inoculum and mild or asymptomatic disease with SARS-CoV-2 in light of population-level masking has received little attention so this is one of the first perspectives to discuss the evidence supporting this theory.

An Overview on the Role of Relative Humidity in Airborne Transmission of SARS-CoV-2 in Indoor Environments

COVID-19 disease is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which originated in Wuhan, China and spread with an astonishing rate across the world. The transmission routes of SARS-CoV-2 are still debated, but recent evidence strongly suggests that COVID-19 could be transmitted via air in poorly ventilated places. Some studies also suggest the higher surface stability of SARS-CoV-2 as compared to SARS-CoV-1. It is also possible that small viral particles may enter into indoor environments from the various emission sources aided by environmental factors such as relative humidity, wind speed, temperature, thus representing a type of an aerosol transmission. Here, we explore the role of relative humidity in airborne transmission of SARS-CoV-2 virus in indoor environments based on recent studies around the world. Humidity affects both the evaporation kinematics and particle growth. In dry indoor places i.e., less humidity (< 40% RH), the chances of airborne transmission of SARS-CoV-2 are higher than that of humid places (i.e., > 90% RH). Based on earlier studies, a relative humidity of 40–60% was found to be optimal for human health in indoor places. Thus, it is extremely important to set a minimum relative humidity standard for indoor environments such as hospitals, offices and public transports for minimization of airborne spread of SARS-CoV-2.

COVID-19 mortality in Lombardy: the vulnerability of the oldest old and the resilience of male centenarians

Italy was the first European nation to be affected by COVID-19. The biggest cluster of cases occurred in Lombardy, the most populous Italian region, and elderly men were the population hit in the hardest way. Besides its high infectivity, COVID-19 causes a severe cytokine storm and old people, especially those with comorbidities, appear to be the most vulnerable, presumably in connection to inflammaging. In centenarians inflammaging is much lower than predicted by their chronological age and females, presenting survival advantage in almost all centenarian populations, outnumber males, a phenomenon particularly evident in Northern Italy. Within this scenario, we wondered if: a) the COVID-19 mortality in centenarians was lower than that in people aged between 50 and 80 and b) the mortality from COVID-19 in nonagenarians and centenarians highlighted gender differences.We checked COVID-19-related vulnerability/mortality at the peak of infection (March 2020), using data on total deaths (i.e. not only confirmed COVID-19 cases). Our conclusion is that excess mortality increases steadily up to very old ages and at the same time men older than 90 years become relatively more resilient than age-matched females.

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Genetic and Phenotypic Evidence for the Causal Relationship Between Aging and COVID-19

Kejun Ying, Ranran Zhai, Timothy V Pyrkov, Marco Mariotti, Peter O Fedichev, Xia Shen, Vadim N Gladyshev

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Abstract

Epidemiological studies have revealed that the elderly and those with co-morbidities are most susceptible to COVID-19. To understand the genetic link between aging and the risk of COVID-19, we conducted a multi-instrument Mendelian randomization analysis and found that the genetic variation that leads to a longer lifespan is significantly associated with a lower risk of COVID-19 infection. The odds ratio is 0.32 (95% CI: 0.18 to 0.57; $P = 1.3 \times 10^{-4}$) per additional 10 years of life, and 0.62 (95% CI: 0.51 to 0.77; $P = 7.2 \times 10^{-6}$) per unit higher log odds of surviving to the 90th percentile age. On the other hand, there was no association between COVID-19 susceptibility and healthspan (the lifespan free of the top seven age-related morbidities). To examine the relationship at the phenotypic level, we applied various biological aging clock models and detected an association between the biological age acceleration and future incidence and severity of COVID-19 infection for all subjects as well as for the individuals free of chronic disease. Biological age acceleration was also significantly associated with the risk of death in COVID-19 patients. Our findings suggest a causal relationship between aging and COVID-19, defined by genetic variance, the rate of aging, and the burden of chronic diseases.

Moderna's COVID-19 vaccine triggers immune response in older adults

Last month, Moderna posted "robust" phase 1 results for its COVID-19 vaccine in adults up to age 55. Now, it's following up with data from a small group of older adults—and they look promising.

The phase 1 study, being run by the National Institute of Allergy and Infectious Diseases, is testing three dose levels of the vaccine, mRNA-1273, given in two injections a month apart in 120 adults. As seen in 45 younger adults, the middle dose of the vaccine triggered the production of neutralizing antibodies against SARS-CoV-2, the virus that causes COVID-19, in 10 patients aged 56 to 70 and 10 patients over 71. Moderna presented the data on Wednesday at a meeting of the CDC's Advisory Committee on Immunization Practices (ACIP).

The investigators found that the older adults' antibody levels were two to three times higher than those measured in 38 patients who had recovered from COVID-19. Compare that to the results from younger adults—one test found that the middle dose, 100 micrograms, triggered antibody levels that were four times higher than those seen in recovered patients, while a different test found those patients had twice the antibody level of the recovered patients. Whichever way you slice it, it's good news, wrote Jefferies analyst Michael Yee in an investor note at the time.

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ACE2, Metformin, and COVID-19

Atul Malhotra [1], Mark Hepokoski [2], Karen C McCowen [3], John Y-J Shyy [4]

Affiliations + expand

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Free PMC article

Abstract

COVID-19 is becoming a leading cause of mortality throughout the world, and few effective therapies are currently available. Angiotensin converting enzyme 2 (ACE2) is essential to COVID-19 pathogenesis, as the binding of SARS-CoV-2 spike protein (S protein) is required for viral entry and development of COVID-19. ACE2 regulates the protective arm of the renin-angiotensin-aldosterone system (RAAS) that endows anti-hypertensive and anti-inflammatory effects in the cardiovascular and pulmonary systems. Preclinical data suggest ACE2 might be downregulated after SARS-CoV-2 binding, and treatments that increase ACE2 may prevent cardiopulmonary injury. Development, testing, and mass production of novel ACE2 therapies may take years, whereas more effective treatments for COVID-19 are needed urgently. Metformin is a widely available anti-diabetic agent that has an excellent safety profile, and clinical and preclinical data suggest metformin may offer cardiopulmonary protection in COVID-19 via enhanced ACE2 expression.

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METFORMIN USE IS ASSOCIATED WITH REDUCED MORTALITY IN A DIVERSE POPULATION WITH COVID-19 AND DIABETES

BACKGROUND: Coronavirus disease-2019 (COVID-19) is a growing pandemic with an increasing death toll that has been linked to various comorbidities as well as racial disparity. However, the specific characteristics of these at-risk populations are still not known and approaches to lower mortality are lacking. METHODS: We conducted a retrospective electronic health record data analysis of 25,326 subjects tested for COVID-19 between 2/25/20 and 6/22/20 at the University of Alabama at Birmingham Hospital, a tertiary health care center in the racially diverse Southern U.S. The primary outcome was mortality in COVID-19-positive subjects and the association with subject characteristics and comorbidities was analyzed using simple and multiple linear logistic regression. RESULTS: The odds ratio of contracting COVID-19 was disproportionately high in Blacks/African-Americans (OR 2.6; 95%CI 2.19-3.10; p<0.0001) and in subjects with obesity (OR 1.93; 95%CI 1.64-2.28; p<0.0001), hypertension (OR 2.46; 95%CI 2.07-2.93; p<0.0001), and diabetes (OR 2.11; 95%CI 1.78-2.48; p<0.0001). Diabetes was also associated with a dramatic increase in mortality (OR 3.62; 95%CI 2.11-6.2; p<0.0001) and emerged as an independent risk factor in this diverse population even after correcting for age, race, sex, obesity and hypertension. Interestingly, we found that metformin treatment was independently associated with a significant reduction in mortality in subjects with diabetes and COVID-19 (OR 0.33; 95%CI 0.13-0.84; p=0.0210). CONCLUSION: Thus, these results suggest that while diabetes is an independent risk factor for COVID-19-related mortality, this risk is dramatically reduced in subjects taking metformin, raising the possibility that metformin may provide a protective approach in this high risk population.

In-Hospital Use of Statins Is Associated with a Reduced Risk of Mortality among Individuals with COVID-19

Statins are lipid-lowering therapeutics with favorable anti-inflammatory profiles and have been proposed as an adjunct therapy for COVID-19. However, statins may increase the risk of SARS-CoV-2 viral entry by inducing ACE2 expression. Here, we performed a retrospective study on 13,981 patients with COVID-19 in Hubei Province, China, among which 1,219 received statins. Based on a mixed-effect Cox model after propensity score-matching, we found that the risk for 28-day all-cause mortality was 5.2% and 9.4% in the matched statin and non-statin groups, respectively, with an adjusted hazard ratio of 0.58. The statin use-associated lower risk of mortality was also observed in the Cox time-varying model and marginal structural model analysis. These results give support for the completion of ongoing prospective studies and randomized controlled trials involving statin treatment for COVID-19, which are needed to further validate the utility of this class of drugs to combat the mortality of this pandemic.

Early Hydroxychloroquine Administration for Rapid Severe Acute Respiratory Syndrome Coronavirus 2 Eradication

There are no proven therapeutics for Coronavirus disease 2019 (COVID-19) pneumonia outbreak. We observed and analyzed the clinical efficacy of the most used hydroxychloroquine (HCQ) for 30 days. In this study, administration of HCQ <5 days from diagnosis (odds ratio: 0.111, 95% confidence interval: 0.034 - 0.367, *P* = 0.001) was the only protective factor for prolonging of viral shedding in COVID-19 patients. Early administration of HCQ significantly ameliorates inflammatory cytokine secretion by eradicating COVID-19, at discharge. Our findings suggest that patients confirmed of COVID-19 infection should be administrated HCQ as soon as possible.

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

BACKGROUND

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

METHODS

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

RESULTS

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

CONCLUSIONS

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

On-target versus off-target effects of drugs inhibiting the replication of SARS-CoV-2

The current epidemic of coronavirus disease-19 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) calls for the development of inhibitors of viral replication. Here, we performed a bioinformatic analysis of published and purported SARS-CoV-2 antivirals including imatinib mesylate that we found to suppress SARS-CoV-2 replication on Vero E6 cells and that, according to the published literature on other coronaviruses is likely to act on-target, as a tyrosine kinase inhibitor. We identified a cluster of SARS-CoV-2 antivirals with characteristics of lysosomotropic agents, meaning that they are lipophilic weak bases capable of penetrating into cells. These agents include cepharentine, chloroquine, chlorpromazine, clemastine, cloperastine, emetine, hydroxychloroquine, haloperidol, ML240, PB28, ponatinib, siramesine, and zotatifin (eFT226) all of which are likely to inhibit SARS-CoV-2 replication by non-specific (off-target) effects, meaning that they probably do not act on their 'official' pharmacological targets, but rather interfere with viral replication through non-specific effects on acidophilic organelles including autophagosomes, endosomes, and lysosomes. Imatinib mesylate did not fall into this cluster. In conclusion, we propose a tentative classification of SARS-CoV-2 antivirals into specific (on-target) versus non-specific (off-target) agents based on their physicochemical characteristics.

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Predicting novel drugs for SARS-CoV-2 using machine learning from a >10 million chemical space

There is an urgent need for the identification of effective therapeutics for COVID-19 and we have developed a machine learning drug discovery pipeline to identify several drug candidates. First, we collect assay data for 65 target human proteins known to interact with the SARS-CoV-2 proteins, including the ACE2 receptor. Next, we train machine learning models to predict inhibitory activity and use them to screen FDA registered chemicals and approved drugs (~100,000) and ~14 million purchasable chemicals. We filter predictions according to estimated mammalian toxicity and vapor pressure. Prospective volatile candidates are proposed as novel inhaled therapeutics since the nasal cavity and respiratory tracts are early bottlenecks for infection. We also identify candidates that act across multiple targets as promising for future analyses. We anticipate that this theoretical study can accelerate testing of two categories of therapeutics: repurposed drugs suited for short-term approval, and novel efficacious drugs suitable for a long-term follow up.

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A public health perspective of aging: do hyper-inflammatory syndromes such as COVID-19, SARS, ARDS, cytokine storm syndrome, and post-ICU syndrome accelerate short- and long-term inflammaging?

A central clinical question as the world deals with the COVID-19 pandemic is what the long-term sequelae for the millions of individuals will be who recover from the hyperinflammatory state characterizing COVID-19 and in particular for the hundreds of thousands who are ill enough to need hospitalization and in particular ICU care. Even when the pandemic is finally controlled, will COVID-19 survivors face exaggerated internal inflammatory processes, worsening co-morbidities, and increased susceptibility to age-related diseases? Clues for what may happen in post-COVID-19 patients can be elicited from those who recovered from other conditions that lead to similar hyperinflammatory states such as Severe Acute Respiratory Syndrome (SARS), acute respiratory disease syndrome (ARDS), cytokine storm syndrome, and post-ICU syndrome. The short-and long-term sequalae following recovery from each of these conditions suggests that these syndromes lead to an accelerated state of chronic subclinical systemic inflammation often seen in aging (termed inflammaging) resulting in increased and worsening age-related conditions including frailty even in younger individuals.

Lung and gut microbiota are altered by hyperoxia and contribute to oxygen-induced lung injury in mice

Inhaled oxygen, although commonly administered to patients with respiratory disease, causes severe lung injury in animals and is associated with poor clinical outcomes in humans. The relationship between hyperoxia, lung and gut microbiota, and lung injury is unknown. Here, we show that hyperoxia conferred a selective relative growth advantage on oxygen-tolerant respiratory microbial species (e.g., *Staphylococcus aureus*) as demonstrated by an observational study of critically ill patients receiving mechanical ventilation and experiments using neonatal and adult mouse models. During exposure of mice to hyperoxia, both lung and gut bacterial communities were altered, and these communities contributed to oxygen-induced lung injury. Disruption of lung and gut microbiota preceded lung injury, and variation in microbial communities correlated with variation in lung inflammation. Germ-free mice were protected from oxygen-induced lung injury, and systemic antibiotic treatment selectively modulated the severity of oxygen-induced lung injury in conventionally housed animals. These results suggest that inhaled oxygen may alter lung and gut microbial communities and that these communities could contribute to lung injury.

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News Feature | Published: 11 August 2020

A singular view of COVID-19

Michael Eisenstein

Nature Biotechnology **38**, 1016–1020(2020) | Cite this article

Single-cell analysis sheds light on immune response to COVID-19 infection, enables the rapid discovery of antibody leads, and points to ways to get ahead of future pandemics.

In late January, Xiaoliang Sunney Xie was in Davos, Switzerland, attending the World Economic Forum – but his mind was miles away, contemplating the coronavirus outbreak raging in his homeland. "Wuhan was locked down," says Xie, Director of the Beijing Advanced Innovation Center for Genomics at Peking University, "and at that time, the situation in China was very serious." Shortly after he returned on 25 January, he and his colleague were already contemplating a clinical research program to isolate potent neutralizing antibodies against SARS-CoV-2, and by 2 February, his team had coordinated with Beijing Youan Hospital to arrange access to patients who had beaten COVID-19.

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Unity's efforts do not age well

Joanne Fagg

Amy Brown

Research into biological pathways associated with ageing has attracted much attention, and funding, but much work remains early and in the hands of private companies. With a focus on "senolytics" and a Nasdaq listing, Unity Biotech represented a rare opportunity for investors to dabble in this nascent field, though the failure of the company's only clinical-stage candidate shows that this remains high-risk. UBX0101 was being tested in moderate to severe painful osteoarthritis of the knee; a phase II study found no statistically significant difference between any treatment arm and placebo. The primary endpoint was Womac-A, a questionnaire to assess pain, and the company blamed an unusually large placebo effect for the outcome. Unity's focus is senescent cells, which have stopped dividing and have been linked to a number of age-related diseases. UBX0101 was said to inhibit MDM2/p53 protein interaction, which the company claimed could eliminate senescent cells. A second project, UBX1325, is expected to enter the clinic in ophthalmology later this year. This has a different mechanism, targeting an apoptosis regulatory protein, Bcl-xL, but the 62% plunge in Unity stock this morning suggests that little confidence remains in the company's approach.

Unity's phase II failure (NCT04129944)		
UBX0101 arm	**Placebo-adjusted change**	**P value**
0.5mg (n = 45)	0.093	0.5222
2.0mg (n = 46)	-0.035	0.8069
4.0mg (n = 46)	-0.002	0.987
Primary endpoint: change from baseline in Womac-A (0-4 scale) at week 12. Source: press release.		

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WORLD VIEW · 25 AUGUST 2020

Confusion over Europe's data-protection law is stalling scientific progress

Two steps will help collaborations worldwide to share information and comply with EU privacy rules.

The GDPR has stalled at least 40 clinical and observational studies on risk factors and exposures for cancer. The NIH's Clinical Center in Bethesda, Maryland, is unable to secure European donor samples for experimental blood-stem-cell transplants aimed at treating otherwise intractable cancers. A 25-year-old diabetes study was derailed for 18 months – it took top-level intervention to move forward, and remains the only data-sharing agreement reached between the NIH and a European counterpart since the enactment of the GDPR.

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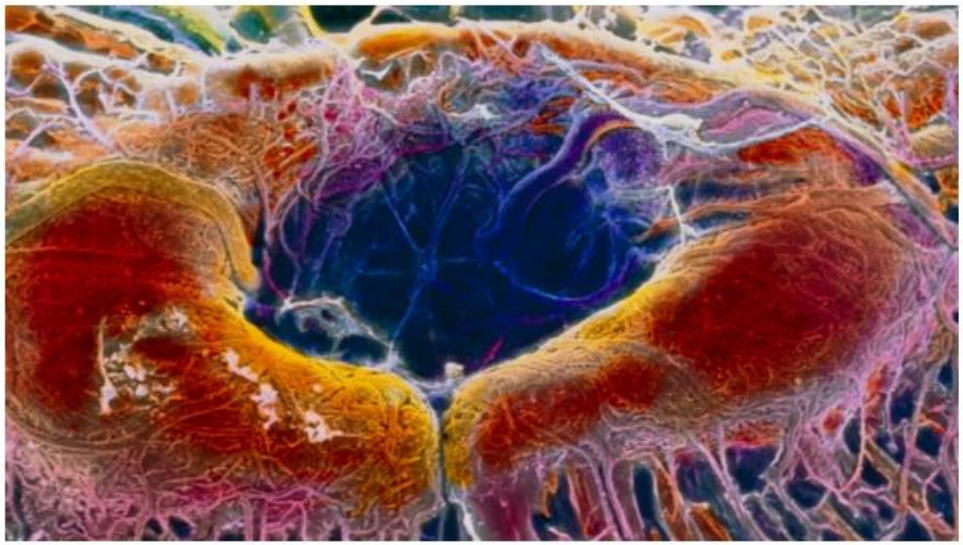
CRISPR treatment inserted directly into the body for first time

Experiment tests a gene-editing therapy for a hereditary blindness disorder.

Heidi Ledford



The human retina: a CRISPR therapy has been inserted directly into a person for the first time — in the eye. Prof. P. Motta/Dept. of Anatomy/University La Sapienza of Rome/SPL

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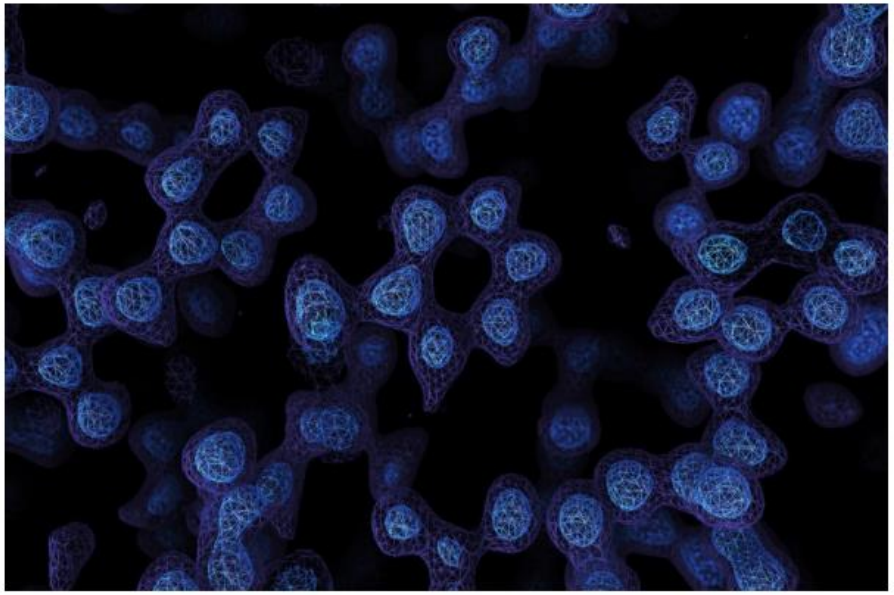
‘It opens up a whole new universe’: Revolutionary microscopy technique sees individual atoms for first time

Cryo-electron microscopy breaks a key barrier that will allow the workings of proteins to be probed in unprecedented detail.

Ewen Callaway



A Cryo-EM map of the protein apoferritin. Credit: Paul Emsley/MRC Laboratory of Molecular Biology

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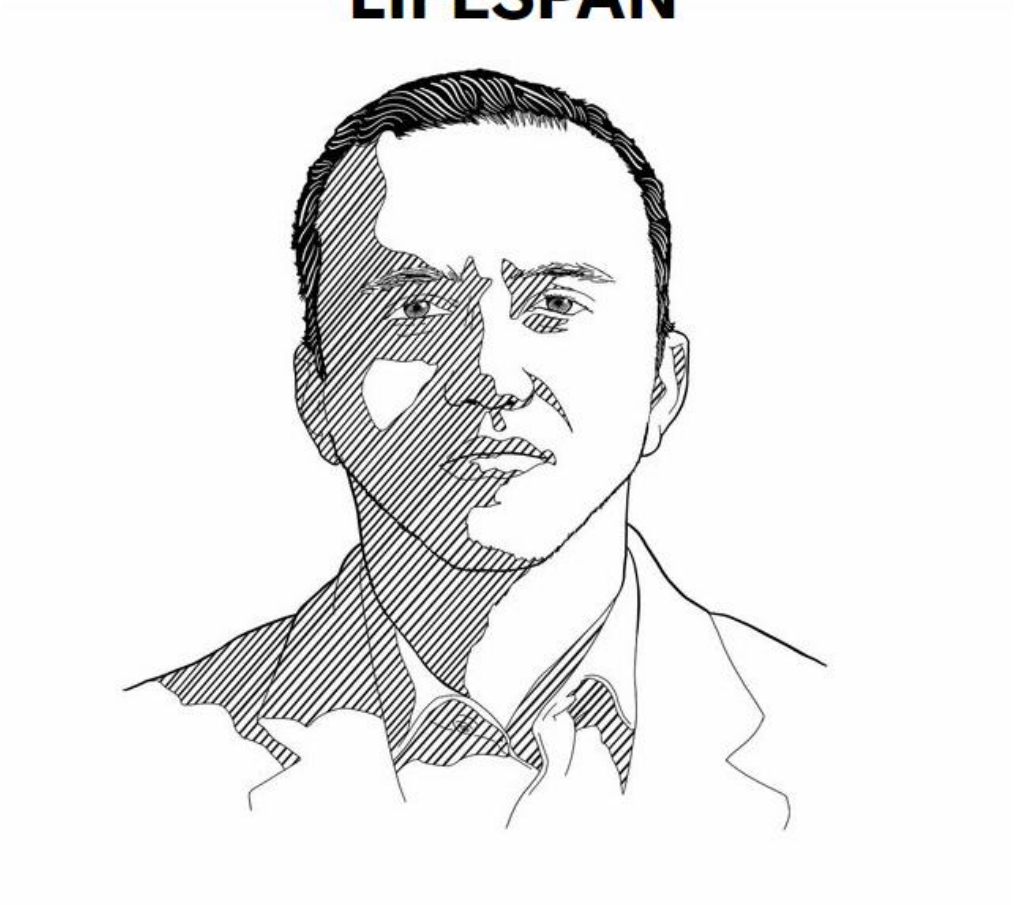
INCREASING HUMAN'S LIFESPAN



9. JULI 2020

These are the Top 5 European Longevity Focused Investment Funds – a commentary by Sergey Balasanyan, CEO of Longevity Card UK & EU and Co-Founder of Longevity Bank project.

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Atomwise raises $123M to expand AI-powered drug design efforts

by Conor Hale | Aug 14, 2020 11:35am

The series B proceeds will help Atomwise build up its own internal portfolio of small molecule drug candidates, aimed at "historically undruggable" disease targets. (UCSF)

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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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Similar burden of pathogenic coding variants in exceptionally long-lived individuals and individuals without exceptional longevity

Centenarians (exceptionally long-lived individuals—ELLI) are a unique segment of the population, exhibiting long human lifespan and healthspan, despite generally practicing similar lifestyle habits as their peers. We tested disease-associated mutation burden in ELLI genomes by determining the burden of pathogenic variants reported in the ClinVar and HGMD databases using data from whole exome sequencing (WES) conducted in a cohort of ELLI, their offspring, and control individuals without antecedents of familial longevity (n = 1879), all descendent from the founder population of Ashkenazi Jews. The burden of pathogenic variants did not differ between the three groups. Additional analyses of variants subtypes and variant effect predictor (VEP) biotype frequencies did not reveal a decrease of pathogenic or loss-of-function (LoF) variants in ELLI and offspring compared to the control group. Case–control pathogenic variants enrichment analyses conducted in ELLI and controls also did not identify significant differences in any of the variants between the groups and polygenic risk scores failed to provide a predictive model. Interestingly, cancer and Alzheimer's disease-associated variants were significantly depleted in ELLI compared to controls, suggesting slower accumulation of mutation. That said, polygenic risk score analysis failed to find any predictive variants among the functional variants tested. The high similarity in the burden of pathogenic variation between ELLI and individuals without familial longevity supports the notion that extension of lifespan and healthspan in ELLI is not a consequence of pathogenic variant depletion but rather a result of other genomic, epigenomic, or potentially nongenomic properties.

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Senolytics prevent mt-DNA-induced inflammation and promote the survival of aged organs following transplantation

Older organs represent an untapped potential to close the gap between demand and supply in organ transplantation but are associated with age-specific responses to injury and increased immunogenicity, thereby aggravating transplant outcomes. Here we show that cell-free mitochondrial DNA (cf-mt-DNA) released by senescent cells accumulates with aging and augments immunogenicity. Ischemia reperfusion injury induces a systemic increase of cf-mt-DNA that promotes dendritic cell-mediated, age-specific inflammatory responses. Comparable events are observed clinically, with the levels of cf-mt-DNA elevated in older deceased organ donors, and with the isolated cf-mt-DNA capable of activating human dendritic cells. In experimental models, treatment of old donor animals with senolytics clear senescent cells and diminish cf-mt-DNA release, thereby dampening age-specific immune responses and prolonging the survival of old cardiac allografts comparable to young donor organs. Collectively, we identify accumulating cf-mt-DNA as a key factor in inflamm-aging and present senolytics as a potential approach to improve transplant outcomes and availability.

Accelerated aging among childhood, adolescent, and young adult cancer survivors is evidenced by increased expression of p16INK4a and frailty

Background

Cellular senescence, measured by expression of the cell cycle kinase inhibitor $p16^{INK4a}$, may contribute to accelerated aging in survivors of childhood, adolescent, and young adult cancer. The authors measured peripheral blood T-lymphocyte $p16^{INK4a}$ expression among pediatric and young adult cancer survivors, hypothesizing that $p16^{INK4a}$ expression is higher after chemotherapy and among frail survivors.

Methods

A cross-sectional cohort of young adult survivors and age-matched, cancer-free controls were assessed for $p16^{INK4a}$ expression and frailty. Newly diagnosed pediatric patients underwent prospective measurements of $p16^{INK4a}$ expression before and after cancer therapy. Frailty was measured with a modified Fried frailty phenotype evaluating sarcopenia, weakness, slowness, energy expenditure, and exhaustion.

Results

The cross-sectional cohort enrolled 60 survivors and 29 age-matched controls with a median age of 21 years (range, 17-29 years). The prospective cohort enrolled 9 newly diagnosed patients (age range, 1-18 years). Expression of $p16^{INK4a}$ was higher among survivors compared with controls (9.6 vs 8.9 $\log_2$ p16 units; 2-sided $P = .005$, representing a 25-year age acceleration in survivors) and increased among newly diagnosed patients from matched pretreatment to posttreatment samples (7.3-8.9 $\log_2$ p16 units; 2-sided $P = .002$). Nine survivors (16%) were frail and had higher $p16^{INK4a}$ expression compared with robust survivors (10.5 [frail] vs 9.5 [robust] $\log_2$ p16 units; 2-sided $P = .055$), representing a 35-year age acceleration among frail survivors.

Conclusions

Chemotherapy is associated with increased cellular senescence and molecular age in pediatric and young adult cancer survivors. Frail survivors, compared with robust survivors, exhibit higher levels of $p16^{INK4a}$, suggesting that cellular senescence may be associated with early aging in survivors.

Rapid senescence-like response after acute injury

Xiaogang Chu, Jin Wen, Raghavan Pillai Raju

Cellular senescence is a state of irreversible growth arrest. Short-term programmed senescence such as in embryonic development and slowly progressing senescence as in aging are both well described. However, acute senescence in living organisms is not well understood. We hypothesized that hemorrhagic shock injury (HI) caused by whole body hypoxia and nutrient deprivation, resulting in organ dysfunction due to severe blood loss, could lead to acute senescence in vivo. Our experiments, for the first time, demonstrate a rapidly emerged, senolytics-responsive, senescence-like response in the rat liver in less than five hr following hemorrhagic shock. We conclude that the senescence, or pseudosenescence, observed is necessary to maintain tissue homeostasis following the injury.

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Doxorubicin generates senescent microglia that exhibit altered proteomes, higher levels of cytokine secretion, and a decreased ability to internalize amyloid β

Cellular senescence is defined by irreversible cell-cycle arrest and is an evolutionarily conserved hallmark of aging. In this study, we generate senescent microglial cells via exposure to the chemotherapy drug doxorubicin. Compared to control cells, doxorubicin-treated microglia exhibited an altered morphology characterized by an enlarged cell size, a flattened appearance, and the development of prominent filaments. Senescent cells harbored elevated levels of senescence associated-β-galactosidase, $p16^{Ink4a}$, and γ-H2AX. Senescent microglia were also less efficient at internalizing amyloid β and pHrodo bioparticles. A detailed proteomic analysis using SWATH-MS identified 201 proteins that were significantly downregulated and 127 that were significantly upregulated in doxorubicin-treated microglia. Proteins involved in processes such as protein synthesis, RNA damage and repair, and protein degradation were largely downregulated while those compromising the integrity of the cell were predominantly upregulated. Various proteins involved in proteasomal processing were among the most significantly downregulated in senescent cells. Relevant to the deleterious senescence-associated secretory phenotype, senescent cells secreted higher levels of the inflammatory cytokines IL-6, IL-8, TNF-α, and GRO-α. Our data suggest that symptoms of brain aging and age-related neurodegenerative disease may be partially caused by defective phagocytosis, impaired proteasomal processing, and elevated cytokine secretion of senescent microglia.

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Non-canonical ATM/MRN activities temporally define the senescence secretory program

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Senescent cells display senescence-associated (SA) phenotypic programs such as stable proliferation arrest (SAPA) and a secretory phenotype (SASP). Senescence-inducing persistent DNA double-strand breaks (pDSBs) cause an immediate DNA damage response (DDR) and SAPA, but the SASP requires days to develop. Here, we show that following the immediate canonical DDR, a delayed chromatin accumulation of the ATM and MRN complexes coincides with the expression of SASP factors. Importantly, histone deacetylase inhibitors (HDACi) trigger SAPA and SASP in the absence of DNA damage. However, HDACi-induced SASP also requires ATM/MRN activities and causes their accumulation on chromatin, revealing a DNA damage-independent, non-canonical DDR activity that underlies SASP maturation. This non-canonical DDR is required for the recruitment of the transcription factor NF-κB on chromatin but not for its nuclear translocation. Non-canonical DDR further does not require ATM kinase activity, suggesting structural ATM functions. We propose that delayed chromatin recruitment of SASP modulators is the result of non-canonical DDR signaling that ensures SASP activation only in the context of senescence and not in response to transient DNA damage-induced proliferation arrest.

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Lamin A safeguards the m^{6}A methylase METTL14 nuclear speckle reservoir to prevent cellular senescence

Mutations in *LMNA* gene are frequently identified in patients suffering from a genetic disorder known as Hutchison–Gilford progeria syndrome (HGPS), providing an ideal model for the understanding of the mechanisms of aging. Lamin A, encoded by *LMNA*, is an essential component of the subnuclear domain–nuclear speckles; however, the functional significance in aging is unclear. Here, we show that Lamin A interacts with the m^{6}A methyltransferases, METTL3 and METTL14 in nuclear speckles. Lamin A deficiency compromises the nuclear speckle METTL3/14 reservoir and renders these methylases susceptible to proteasome-mediated degradation. Moreover, METTL3/14 levels progressively decline in cells undergoing replicative senescence. Overexpression of *METTL14* attenuates both replicative senescence and premature senescence. The data reveal an essential role for Lamin A in safeguarding the nuclear speckle reservoir of the m^{6}A methylase METTL14 to antagonize cellular senescence.

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Multiparameter flow cytometric detection and quantification of senescent cells *in vitro*

Adeolu Badi Adewoye, Dimitris Tampakis, Antonia Follenzi & Alexandra Stolzing

It has been over half a century since cellular senescence was first noted and characterized, and yet no consensus senescent marker has been reliably established. This challenge is compounded by the complexity and heterogenic phenotypes of senescent cells. This necessitates the use of multiple biomarkers to confidently characterise senescent cells. Despite cytochemical staining of senescence associated-beta-galactosidase being a single marker approach, as well as being time and labour-intensive, it remains the most popular detection method. We have developed an alternative flow cytometry-based method that simultaneously quantifies multiple senescence markers at a single-cell resolution. In this study, we applied this assay to the quantification of both replicative and induced senescent primary cells. Using this assay, we were able to quantify the activity level of SA β-galactosidase, the expression level of $p16^{INK4a}$ and γH2AX in these cell populations. Our results show this flow cytometric approach to be sensitive, robust, and consistent in discriminating senescent cells in different cell senescence models. A strong positive correlation between these commonly- used senescence markers was demonstrated. The method described in this paper can easily be scaled up to accommodate high-throughput screening of senescent cells in applications such as therapeutic cell preparation, and in therapy-induced senescence following cancer treatment.

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Real-Time In Vivo Detection of Cellular Senescence through the Controlled Release of the NIR Fluorescent Dye Nile Blue

In vivo detection of cellular senescence is accomplished by using mesoporous silica nanoparticles loaded with the NIR-FDA approved Nile blue (NB) dye and capped with a galactohexasaccharide (**S3**). NB emission at 672 nm is highly quenched inside **S3**, yet a remarkable emission enhancement is observed upon cap hydrolysis in the presence of β-galactosidase and dye release. The efficacy of the probe to detect cellular senescence is tested in vitro in melanoma SK-Mel-103 and breast cancer 4T1 cells and in vivo in palbociclib-treated BALB/cByJ mice bearing breast cancer tumor.

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A bioluminescent probe for longitudinal monitoring of mitochondrial membrane potential

Arkadiy A. Bazhin, Riccardo Sinisi, Umberto De Marchi, Aurélie Hermant, Nicolas Sambiagio, Tamara Maric, Ghyslain Budin & Elena A. Goun

Mitochondrial membrane potential ($\Delta\Psi_m$) is a universal selective indicator of mitochondrial function and is known to play a central role in many human pathologies, such as diabetes mellitus, cancer and Alzheimer's and Parkinson's diseases. Here, we report the design, synthesis and several applications of mitochondria-activatable luciferin (MAL), a bioluminescent probe sensitive to $\Delta\Psi_m$, and partially to plasma membrane potential ($\Delta\Psi_p$), for non-invasive, longitudinal monitoring of $\Delta\Psi_m$ in vitro and in vivo. We applied this new technology to evaluate the aging-related change of $\Delta\Psi_m$ in mice and showed that nicotinamide riboside (NR) reverts aging-related mitochondrial depolarization, revealing another important aspect of the mechanism of action of this potent biomolecule. In addition, we demonstrated application of the MAL probe for studies of brown adipose tissue (BAT) activation and non-invasive in vivo assessment of $\Delta\Psi_m$ in animal cancer models, opening exciting opportunities for understanding the underlying mechanisms and for discovery of effective treatments for many human pathologies.

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Alpha-Ketoglutarate, an Endogenous Metabolite, Extends Lifespan and Compresses Morbidity in Aging Mice

Metabolism and aging are tightly connected. Alpha-ketoglutarate is a key metabolite in the tricarboxylic acid (TCA) cycle, and its levels change upon fasting, exercise, and aging. Here, we investigate the effect of alpha-ketoglutarate (delivered in the form of a calcium salt, CaAKG) on healthspan and lifespan in C57BL/6 mice. To probe the relationship between healthspan and lifespan extension in mammals, we performed a series of longitudinal, clinically relevant measurements. We find that CaAKG promotes a longer, healthier life associated with a decrease in levels of systemic inflammatory cytokines. We propose that induction of IL-10 by dietary AKG suppresses chronic inflammation, leading to health benefits. By simultaneously reducing frailty and enhancing longevity, AKG, at least in the murine model, results in a compression of morbidity.

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Transcriptome analysis of mouse aortae reveals multiple novel pathways regulated by aging

Vascular aging has been documented as a vital process leading to arterial dysfunction and age-related cardiovascular and cerebrovascular diseases. However, our understanding of the molecular underpinnings of age-related phenotypes in the vascular system is incomplete. Here we performed bulk RNA sequencing in young and old mouse aortae to elucidate age-associated changes in the transcriptome. Results showed that the majority of upregulated pathways in aged aortae relate to immune response, including inflammation activation, apoptotic clearance, and phagocytosis. The top downregulated pathway in aged aortae was extracellular matrix organization. Additionally, protein folding control and stress response pathways were downregulated in the aged vessels, with an array of downregulated genes encoding heat shock proteins (HSPs). We also found that circadian core clock genes were differentially expressed in young versus old aortae. Finally, transcriptome analysis combined with protein expression examination and smooth muscle cell (SMC) lineage tracing revealed that SMCs in aged aortae retained the differentiated phenotype, with an insignificant decrease in SMC marker gene expression. Our results therefore unveiled critical pathways regulated by arterial aging in mice, which will provide important insight into strategies to defy vascular aging and age-associated vascular diseases.

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Genome-wide transcript and protein analysis reveals distinct features of aging in the mouse heart

Understanding the molecular mechanisms underlying age-related changes in the heart is challenging due to the contributions from numerous genetic and environmental factors. Genetically diverse outbred mice provide a model to study the genetic regulation of aging processes in healthy tissues from individuals undergoing natural aging in a controlled environment. We analyzed transcriptome and proteome data from outbred mice at 6, 12 and 18 months of age to reveal a scenario of cardiac hypertrophy, fibrosis, extracellular matrix remodeling, and reemergence of fetal gene expression patterns. We observed widespread changes in protein trafficking and sorting, and post-translational disruption of the stoichiometry of the protein quality control system itself. We identified genome hotspots of age-by-genetic effects that regulate proteins from the proteasome and endoplasmic reticulum stress response, suggesting that genetic variation in these modules may contribute to individual variation in the aging heart.

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Identification of common cardiometabolic alterations and deregulated pathways in mouse and pig models of aging

Aging is the main risk factor for cardiovascular and metabolic diseases, which have become a global concern as the world population ages. These diseases and the aging process are exacerbated in Hutchinson–Gilford progeria syndrome (HGPS or progeria). Here, we evaluated the cardiometabolic disease in animal models of premature and normal aging with the aim of identifying alterations that are shared or specific to each condition. Despite differences in body composition and metabolic markers, prematurely and normally aging mice developed heart failure and similar cardiac electrical abnormalities. High-throughput proteomics of the hearts of progeric and normally aged mice revealed altered protein oxidation and glycation, as well as dysregulated pathways regulating energy metabolism, proteostasis, gene expression, and cardiac muscle contraction. These results were corroborated in the hearts of progeric pigs, underscoring the translational potential of our findings, which could help in the design of strategies to prevent or slow age-related cardiometabolic disease.

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Proteomic and transcriptomic profiling reveal different aspects of aging in the kidney

The kidney is an excellent model for studying organ aging. Kidney function shows steady decline with age and is easy to assay using urine or blood samples. However, little is known about the molecular changes that take place in the kidney during the aging process. In order to better understand the molecular changes that occur with age, we measured mRNA and protein levels in 188 genetically diverse mice at ages 6, 12, and 18 months. We observed distinctive change in mRNA and protein levels as a function of age. Changes in both mRNA and protein are associated with increased immune infiltration and decreases in mitochondrial function. Proteins show a greater extent of change and reveal changes in a wide array of biological processes including unique, organ-specific features of aging in kidney. Most importantly, we observed functionally important age-related changes in protein that occur in the absence of corresponding changes in mRNA. Our findings suggest that mRNA profiling alone provides an incomplete picture of molecular aging in the kidney and that examination of changes in proteins is essential to understand aging processes that are not transcriptionally regulated.

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A comprehensive transcriptome signature of murine hematopoietic stem cell aging

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Summary

To determine whether a consistent pattern of transcriptional deregulation in aging murine hematopoietic stem cells (HSC) exists, we collected all available transcriptome studies of aged HSCs, adding our own unpublished data. Cross-validation of all datasets identified a core list of consistently differentially expressed genes; the HSC aging signature. Despite heterogeneity between individual studies, the aging signature is robust and has reached saturation. Our analysis also indicates that HSCs become transcriptionally activated upon aging. Unexpectedly, the signature consists largely of membrane-associated transcripts, including many cell surface molecules previously not associated with HSC biology. We validated that *Selp*, the top aging gene, is not only a marker for aged HSCs but is functionally involved in age-associated HSC functional decline. We share the aging signature as an online resource with the community and demonstrate its value by confirming that exposure to sympathomimetics, and deletion of Dnmt3a/b, molecularly resembles HSC rejuvenation or aging, respectively.

The Molecular Landscape of the Aging Mouse Liver

Systems biology approaches often use networks of gene expression and metabolite data to identify regulatory factors and pathways connected with phenotypic variance. Separating upstream causal mechanisms, downstream biomarkers, and incidental correlations remains a significant challenge, yet it is essential for designing mechanistic experiments. To address this, we first designed a population following 2157 individual mice from 89 isogenic strains of BXD mice across their lifespans to identify molecular interactions between genotype, environment, age (GxExA) and metabolic fitness. Each strain was separated into two cohorts, fed low fat (6% cal/fat) or high fat (60% cal/fat) diets. One-third of individuals (662) were sacrificed at ~6, 12, 18, or 24 months-of-age, with the remainder monitored until natural death. Transcriptome, proteome, and metabolome profiles were generated from liver samples. These multi-omic measurements were deconvolved into metabolic networks, where we observed varying network connectivity as a function of GxExA. The multiple independent study variables permitted causal inference analysis for the network variants using stability selection. This calculates the strength and directionality of the interactions between molecular measurements and metabolic networks as a function of age, diet, and genotype, and assigns each gene a score for its relative position to the target pathway. At 1% FDR, 94% of novel connections were stable across age and diet, such as the connection between *Rdh11* with cholesterol biosynthesis and *Mut* with mitochondrial translation. 6% of discovered candidate genes were unstable, indicating a clear causal relationship between the segregating independent variable, the gene, and the pathway. For instance, age drives variation in proteasomal genes (e.g. *Psmb3, Psmb4*), which in turn drive changes in the mitochondrial ribosome. Conversely, COX7A2L malformation drives variation in OXPHOS genes, but both are downstream of changes in mitochondrial translation. Finally, we examined all data for connections with the longevity and known longevity-related pathways, identifying several dozen novel candidate genes. Thus, top two candidates, *Ctsd* and *St7*, had their orthologs knocked down in *C. elegans* and were novelly found to reduce longevity both in wildtype and in mutant long-lived strains.

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Transcriptomic signatures of ageing vary in solitary and social forms of an orchid bee

Eusocial insect queens are remarkable in their ability to maximise both fecundity and longevity, thus escaping the typical trade-off between these two traits. In species exhibiting complex eusocial behaviour, several mechanisms have been proposed to underlie the remoulding of the trade-off, such as reshaping of the juvenile hormone pathway, or caste-specific susceptibility to oxidative stress. However, it remains a challenge to disentangle the molecular mechanisms underlying the remoulding of the trade-off in eusocial insects from caste-specific physiological attributes that have subsequently arisen due to their different life histories. Socially plastic species such as the orchid bee *Euglossa viridissima* represent excellent models to address the role of sociality *per se* in longevity as they allow direct comparisons of solitary and social individuals within a common genetic background. We present data on gene expression and juvenile hormone levels from young and old bees, from both solitary and social nests. We found 940 genes to be differentially expressed with age in solitary females, *versus* only 14 genes in social dominant females, and seven genes in subordinate females. We performed a weighted gene co-expression network analysis to further highlight candidate genes related to ageing in this species. Primary "ageing gene" candidates were related to protein synthesis, gene expression, immunity and venom production. Remarkably, juvenile hormone titres did not vary with age or social status. These results represent an important step in understanding the proximate mechanisms underlying the remodeling of the fecundity/longevity trade-off that accompanies the evolutionary transition from solitary life to eusociality.

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An Integrative Analysis of the Age-Associated Genomic, Transcriptomic and Epigenetic Landscape across Cancers

Age is the most important risk factor for cancer, as cancer incidence and mortality increase with age. However, how molecular alterations in tumours differ among patients of different age remains largely unexplored. Here, using data from The Cancer Genome Atlas, we comprehensively characterised genomic, transcriptomic and epigenetic alterations in relation to patients' age across cancer types. We showed that tumours from older patients present an overall increase in genomic instability, somatic copy-number alterations (SCNAs) and somatic mutations. Age-associated SCNAs and mutations were identified in several cancer-driver genes across different cancer types. The largest age-related genomic differences were found in gliomas and endometrial cancer. We identified age-related global transcriptomic changes and demonstrated that these genes are controlled by age-associated DNA methylation changes. This study provides a comprehensive view of age-associated alterations in cancer and underscores age as an important factor to consider in cancer research and clinical practice.

Telomerase treatment prevents lung profibrotic pathologies associated with physiological aging

Sergio Piñeiro-Hermida, Chiara Autilio, Paula Martínez, Fátima Bosch, Jesús Pérez-Gil, Maria A. Blasco

Short/dysfunctional telomeres are at the origin of idiopathic pulmonary fibrosis (IPF) in patients mutant for telomere maintenance genes. However, it remains unknown whether physiological aging leads to short telomeres in the lung, thus leading to IPF with aging. Here, we find that physiological aging in wild-type mice leads to telomere shortening and a reduced proliferative potential of alveolar type II cells and club cells, increased cellular senescence and DNA damage, increased fibroblast activation and collagen deposits, and impaired lung biophysics, suggestive of a fibrosis-like pathology. Treatment of both wild-type and telomerase-deficient mice with telomerase gene therapy prevented the onset of lung profibrotic pathologies. These findings suggest that short telomeres associated with physiological aging are at the origin of IPF and that a potential treatment for IPF based on telomerase activation would be of interest not only for patients with telomerase mutations but also for sporadic cases of IPF associated with physiological aging.

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Age-induced accumulation of methylmalonic acid promotes tumour progression

The risk of cancer and associated mortality increases substantially in humans from the age of 65 years onwards[1,2,3,4,5,6]. Nonetheless, our understanding of the complex relationship between age and cancer is still in its infancy[2,3,7,8]. For decades, this link has largely been attributed to increased exposure time to mutagens in older individuals. However, this view does not account for the established role of diet, exercise and small molecules that target the pace of metabolic ageing[9,10,11,12]. Here we show that metabolic alterations that occur with age can produce a systemic environment that favours the progression and aggressiveness of tumours. Specifically, we show that methylmalonic acid (MMA), a by-product of propionate metabolism, is upregulated in the serum of older people and functions as a mediator of tumour progression. We traced this to the ability of MMA to induce SOX4 expression and consequently to elicit transcriptional reprogramming that can endow cancer cells with aggressive properties. Thus, the accumulation of MMA represents a link between ageing and cancer progression, suggesting that MMA is a promising therapeutic target for advanced carcinomas.

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MetaboAge DB: a repository of known ageing-related changes in the human metabolome

Teodora Bucaciuc Mracica, Anca Anghel, Catalin Florentin Ion, Corina Violeta Moraru, Robi Tacutu & Gligor Andrei Lazar

Accumulating metabolomics data is starting to become extremely useful in understanding the ageing process, by providing a snapshot into the metabolic state of tissues and organs, at different ages. Molecular studies of such metabolic variations during "normal" ageing can hence guide lifestyle changes and/or medical interventions aimed at improving healthspan and perhaps even lifespan. In this work, we present MetaboAge, a freely accessible database which hosts ageing-related metabolite changes, occurring in healthy individuals. Data is automatically filtered and then manually curated from scientific articles reporting statistically significant associations of human metabolite variations or correlations with ageing. Up to date, MetaboAge contains 408 metabolites annotated with their biological and chemical information, and more than 1515 ageing-related variations, graphically represented on the website grouped by validation methods, sex and age-groups. The MetaboAge database aims to continually structure the expanding information from the field of metabolomics in relation to ageing, thus making it more accessible for further research in gerontology.

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The gut microbiome–derived metabolite trimethylamine *N*-oxide modulates neuroinflammation and cognitive function with aging

Aging is associated with declines in cognitive performance, which are mediated in part by neuroinflammation, characterized by astrocyte activation and higher levels of pro-inflammatory cytokines; however, the upstream drivers are unknown. We investigated the potential role of the gut microbiome–derived metabolite trimethylamine *N*-oxide (TMAO) in modulating neuroinflammation and cognitive function with aging. Study 1: In middle-aged and older humans (65 ± 7 years), plasma TMAO levels were inversely related to performance on NIH Toolbox Cognition Battery tests of memory and fluid cognition (both $r^2 = 0.07$, $p < 0.05$). Study 2: In mice, TMAO concentrations in plasma and the brain increased in parallel with aging ($r^2 = 0.60$), suggesting TMAO crosses the blood-brain barrier. The greater TMAO concentrations in old mice (27 months) were associated with higher brain pro-inflammatory cytokines and markers of astrocyte activation vs. young adult mice (6 months). Study 3: To determine if TMAO independently induces an "aging-like" decline in cognitive function, young mice (6 months) were supplemented with TMAO in chow for 6 months. Compared with controls, TMAO-supplemented mice performed worse on the novel object recognition test, indicating impaired memory and learning, and had increased neuroinflammation and markers of astrocyte activation. Study 4: Human astrocytes cultured with TMAO vs. control media exhibited changes in cellular morphology and protein markers consistent with astrocyte activation, indicating TMAO directly acts on these cells. Our results provide translational insight into a novel pathway that modulates neuroinflammation and cognitive function with aging, and suggest that TMAO might be a promising target for prevention of neuroinflammation and cognitive decline with aging.

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The Gut Virome Database Reveals Age-Dependent Patterns of Virome Diversity in the Human Gut

The gut microbiome profoundly affects human health and disease, and their infecting viruses are likely as important, but often missed because of reference database limitations. Here, we (1) built a human Gut Virome Database (GVD) from 2,697 viral particle or microbial metagenomes from 1,986 individuals representing 16 countries, (2) assess its effectiveness, and (3) report a meta-analysis that reveals age-dependent patterns across healthy Westerners. The GVD contains 33,242 unique viral populations (approximately species-level taxa) and improves average viral detection rates over viral RefSeq and IMG/VR nearly 182-fold and 2.6-fold, respectively. GVD meta-analyses show highly personalized viromes, reveal that inter-study variability from technical artifacts is larger than any "disease" effect at the population level, and document how viral diversity changes from human infancy into senescence. Together, this compact foundational resource, these standardization guidelines, and these meta-analysis findings provide a systematic toolkit to help maximize our understanding of viral roles in health and disease.

Circulating Procollagen Type III N-Terminal Peptide and Physical Function in Adults from the Long Life Family Study

Background

Circulating levels of procollagen type III N-terminal peptide (P3NP) may reflect increased fibrosis of skeletal muscle and other tissues with aging. Herein, we tested if P3NP was associated with baseline and 7-year change in physical function.

Method

Participants (n = 400) were from the Long Life Family Study, a study of exceptional familial longevity. Plasma P3NP concentration was measured using a sandwich enzyme-linked immunosorbent assay (inter-assay coefficient of variation <5.5%). At baseline and 7-year follow-up visits, physical function was measured using the Short Physical Performance Battery (SPPB score 0–12), which consists of gait speed, balance, and chair-rise tests. Grip strength was measured using a handheld dynamometer. The association between log-transformed P3NP and physical function was examined using generalized estimating equations adjusted for familial relatedness, age, sex, height, weight, lifestyle characteristics, liver function, kidney function, lung function, and chronic disease prevalence.

Results

Participants were aged 73.1 ± 15.2 years (range: 39–104), 54% female, had body mass index of 26.6 ± 4.3 kg/m^2, and gait speeds of 1.0 ± 0.3 m/s. One standard deviation higher log-transformed P3NP was related to worse baseline SPPB score ($\beta = -0.9_{points}$), gait speed ($\beta = -0.05_{m/s}$), chair-rises per-second ($\beta = -0.46_{chair\text{-}rises/10\ seconds}$), and grip strength ($\beta = -2.0_{kg}$; all $p < .001$). Higher P3NP was also associated with greater declines in gait speed ($\beta = -1.41$, $p < .001$) and transitioning to being unable to perform chair-rises ($\beta = 0.41$, $p < .001$) after 7 years.

Conclusion

Plasma P3NP may be a strong, novel biomarker of current and future physical function. Future research is needed to extend our findings to other cohorts and determine mechanisms underlying these associations.

Plasma proteomic profile of frailty

Sanish Sathyan, Emmeline Ayers, Tina Gao, Sofiya Milman, Nir Barzilai, Joe Verghese

Frailty is a state of decreased physiological reserve and increased vulnerability to adverse outcomes in aging, and is characterized by dysregulation across various biological pathways. Frailty may manifest biologically as alteration in protein expression, possibly regulated at genetic, transcriptional and epigenetic levels. In this study, we examined the proteomic profile associated with frailty defined by an established cumulative frailty index (FI). Using the SomaScan® assay, 4265 proteins were measured in plasma, of which 55 were positively associated and 88 were negatively associated with the FI. The proteins most strongly associated with frailty were fatty acid-binding proteins, including fatty acid-binding protein (FABP) ($p = 1.96 \times 10^{-19}$) and FABPA ($p = 8.10 \times 10^{-16}$), leptin ($p = 1.43 \times 10^{-14}$), and ANTR2 ($p = 7.95 \times 10^{-20}$). Pathway analysis with the top 143 frailty-associated proteins revealed enrichment for proteins in pathways related to lipid metabolism, musculoskeletal development and function, cell-to-cell signaling and interaction, cellular assembly, and organization. Frailty prediction model constructed with elastic net regression utilizing 110 proteins demonstrated a correlation between predicted frailty and observed frailty ($r = 0.57$, $p < 2.2 \times 10^{-16}$). Predicted frailty was also more strongly correlated with chronological age ($r = 0.54$, $p < 2.2 \times 10^{-16}$) than observed frailty ($r = 0.37$, $p = 1.2 \times 10^{-15}$). This study identified novel proteins and pathways related to frailty that may offer improved frailty phenotyping and prediction.

Kynurenines link chronic inflammation to functional decline and physical frailty

Chronic inflammation is associated with physical frailty and functional decline in older adults; however, the molecular mechanisms of this linkage are not understood. A mouse model of chronic inflammation showed reduced motor function and partial denervation at the neuromuscular junction. Metabolomic profiling of these mice and further validation in frail human subjects showed significant dysregulation in the tryptophan degradation pathway, including decreased tryptophan and serotonin, and increased levels of some neurotoxic kynurenines. In humans, kynurenine strongly correlated with age, frailty status, TNF-αR_1 and IL-6, weaker grip strength, and slower walking speed. To study the effects of elevated neurotoxic kynurenines on motor neuronal cell viability and axonal degeneration, we used motor neuronal cells treated with 3-hydroxykynurenine and quinolinic acid and observed neurite degeneration in a dose-dependent manner and potentiation of toxicity between 3-hydroxykynurenine and quinolinic acid. These results suggest that kynurenines mediate neuromuscular dysfunction associated with chronic inflammation and aging.

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Thymic rejuvenation via FOXN1-reprogrammed embryonic fibroblast (FREF to counteract age-related inflammation

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First published August 13, 2020 - More info

Abstract

Age-associated systemic, chronic inflammation is partially attributed to increased self (auto)-reactivity, resulting from disruption of central tolerance in the aged, involuted thymus. This involution causally results from gradually decreased expression of the transcription factor *FOXN1* in thymic epithelial cells (TECs), while exogenous *FOXN1* in TECs can partially rescue age-related thymic involution. Given the findings that TECs induced from *FOXN1*-overexpressing embryonic fibroblasts can generate an ectopic de novo thymus under the kidney capsule and intra-thymically injected naturally young TECs can lead to middle-aged thymus regrowth, we attempted to extend these two findings by combining them as a novel thymic rejuvenation strategy with two types of promoter-driven (*Rosa26*CreER^T and *FoxN1*Cre) Cre-mediated *FOXN1*-reprogrammed embryonic fibroblasts (FREFs). We engrafted these two-types of FREFs directly into the aged murine thymus. We found significant regrowth of the native aged thymus with rejuvenated architecture and function in both males and females, exhibiting increased thymopoiesis and reinforced thymocyte negative selection, along with reduced senescent T cells and auto-reactive T cell-mediated inflammation in old mice. Therefore, this strategy has preclinical significance and presents a strategy to potentially rescue decreased thymopoiesis and perturbed negative selection to significantly, albeit partially, restore defective central tolerance and reduce subclinical autoimmune symptoms in the elderly.

Inhibition of inflammatory CCR2 signaling promotes aged muscle regeneration and strength recovery after injury

Muscle regeneration depends on a robust albeit transient inflammatory response. Persistent inflammation is a feature of age-related regenerative deficits, yet the underlying mechanisms are poorly understood. Here, we find inflammatory-related CC-chemokine-receptor 2 (Ccr2) expression in non-hematopoietic myogenic progenitors (MPs) during regeneration. After injury, the expression of Ccr2 in MPs corresponds to the levels of its ligands, the chemokines Ccl2, 7, and 8. We find stimulation of Ccr2-activity inhibits MP fusion and contribution to myofibers. This occurs in association with increases in MAPKp38δ/γ signaling, MyoD phosphorylation, and repression of the terminal myogenic commitment factor Myogenin. High levels of Ccr2-chemokines are a feature of regenerating aged muscle. Correspondingly, deletion of *Ccr2* in MPs is necessary for proper fusion into regenerating aged muscle. Finally, opportune Ccr2 inhibition after injury enhances aged regeneration and functional recovery. These results demonstrate that inflammatory-induced activation of Ccr2 signaling in myogenic cells contributes to aged muscle regenerative decline.

Polyploidy in the adult *Drosophila* brain

Long-lived cells such as terminally differentiated postmitotic neurons and glia must cope with the accumulation of damage over the course of an animal's lifespan. How long-lived cells deal with ageing-related damage is poorly understood. Here we show that polyploid cells accumulate in the adult fly brain and that polyploidy protects against DNA damage-induced cell death. Multiple types of neurons and glia that are diploid at eclosion, become polyploid in the adult *Drosophila* brain. The optic lobes exhibit the highest levels of polyploidy, associated with an elevated DNA damage response in this brain region. Inducing oxidative stress or exogenous DNA damage leads to an earlier onset of polyploidy, and polyploid cells in the adult brain are more resistant to DNA damage-induced cell death than diploid cells. Our results suggest polyploidy may serve a protective role for neurons and glia in adult *Drosophila melanogaster* brains.

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Blood substitution therapy rescues the brain of mice from ischemic damage

Acute stroke causes complex, pathological, and systemic responses that have not been treatable by any single medication. In this study, using a murine transient middle cerebral artery occlusion stroke model, a novel therapeutic strategy is proposed, where blood replacement (BR) robustly reduces infarctions and improves neurological deficits in mice. Our analyses of immune cell subsets suggest that BR therapy substantially decreases neutrophils in blood following a stroke. Electrochemiluminescence detection demonstrates that BR therapy reduces cytokine storm in plasma and ELISA demonstrates reduced levels of matrix metalloproteinase-9 (MMP-9) in the plasma and brains at different time points post-stroke. Further, we have demonstrated that the addition of MMP-9 to the blood diminishes the protective effect of the BR therapy. Our study is the first to show that BR therapy leads to profoundly improved stroke outcomes in mice and that the improved outcomes are mediated via MMP-9. These results offer new insights into the mechanisms of stroke damage.

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CMS121, a fatty acid synthase inhibitor, protects against excess lipid peroxidation and inflammation and alleviates cognitive loss in a transgenic mouse model of Alzheimer's disease

The oxidative degradation of lipids has been shown to be implicated in the progression of several neurodegenerative diseases and modulating lipid peroxidation may be efficacious for treating Alzheimer's disease (AD). This hypothesis is strengthened by recent findings suggesting that oxytosis/ferroptosis, a cell death process characterized by increased lipid peroxidation, plays an important role in AD-related toxicities. CMS121 is a small molecule developed against these aspects of neurodegeneration. Here we show that CMS121 alleviates cognitive loss, modulates lipid metabolism and reduces inflammation and lipid peroxidation in the brains of transgenic AD mice. We identify fatty acid synthase (FASN) as a molecular target of CMS121 and demonstrate that modulating lipid metabolism through the inhibition of FASN protects against several AD-related toxicities. These results support the involvement of lipid peroxidation and perturbed lipid metabolism in AD pathophysiology and propose FASN as a target in AD-associated toxicities.

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FOXO3a acts to suppress DNA double-strand break-induced mutations

Ryan R. White, Alexander Y. Maslov, Moonsook Lee, Samantha E. Wilner, Matthew Levy, Jan Vijg

Genomic instability is one of the hallmarks of aging, and both DNA damage and mutations have been found to accumulate with age in different species. Certain gene families, such as sirtuins and the FoxO family of transcription factors, have been shown to play a role in lifespan extension. However, the mechanism(s) underlying the increased longevity associated with these genes remains largely unknown and may involve the regulation of responses to cellular stressors, such as DNA damage. Here, we report that FOXO3a reduces genomic instability in cultured mouse embryonic fibroblasts (MEFs) treated with agents that induce DNA double-strand breaks (DSBs), that is, clastogens. We show that DSB treatment of both primary human and mouse fibroblasts upregulates FOXO3a expression. FOXO3a ablation in MEFs harboring the mutational reporter gene lacZ resulted in an increase in genome rearrangements after bleomycin treatment; conversely, overexpression of human FOXO3a was found to suppress mutation accumulation in response to bleomycin. We also show that overexpression of FOXO3a in human primary fibroblasts decreases DSB-induced γH2AX foci. Knocking out FOXO3a in mES cells increased the frequency of homologous recombination and non-homologous end-joining events. These results provide the first direct evidence that FOXO3a plays a role in suppressing genome instability, possibly by suppressing genome rearrangements.

Short-term calorie restriction enhances DNA repair by non-homologous end joining in mice

Calorie restriction (CR) improves health, reduces cancer incidence and extends lifespan in multiple organisms including mice. CR was shown to enhance base excision repair and nucleotide excision repair pathways of DNA repair, however, whether CR improves repair of DNA double-strand breaks has not been examined in in vivo system. Here we utilize non-homologous end joining (NHEJ) reporter mice to show that short-term CR strongly enhances DNA repair by NHEJ, which is associated with elevated levels of DNA-PK and SIRT6.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Life span extension by glucose restriction is abrogated by methionine supplementation: Cross-talk between glucose and methionine and implication of methionine as a key regulator of life span

Caloric restriction (CR) is known to extend life span across species; however, the molecular mechanisms are not well understood. We investigate the mechanism by which glucose restriction (GR) extends yeast replicative life span, by combining ribosome profiling and RNA-seq with microfluidic-based single-cell analysis. We discovered a cross-talk between glucose sensing and the regulation of intracellular methionine: GR down-regulated the transcription and translation of methionine biosynthetic enzymes and transporters, leading to a decreased intracellular methionine concentration; external supplementation of methionine cancels the life span extension by GR. Furthermore, genetic perturbations that decrease methionine synthesis/uptake extend life span. These observations suggest that intracellular methionine mediates the life span effects of various nutrient and genetic perturbations, and that the glucose-methionine cross-talk is a general mechanism for coordinating the nutrient status and the translation/growth of a cell. Our work also implicates proteasome as a downstream effector of the life span extension by GR.

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Daphnia magna modifies its gene expression extensively in response to caloric restriction revealing a novel effect on haemoglobin isoform preference

Caloric restriction (CR) produces clear phenotypic effects within and between generations of the model crustacean *Daphnia magna*. We have previously established that micro-RNAs and cytosine methylation change in response to CR in this organism, and we demonstrate here that CR has a dramatic effect on gene expression. Over 6,000 genes were differentially expressed between CR and well-fed *D. magna*, with a bias towards up-regulation of genes under caloric restriction. We identified a highly expressed haemoglobin gene that responds to CR by changing isoform proportions. Specifically, a transcript containing three haem-binding erythrocruorin domains was strongly down-regulated under CR in favour of transcripts containing fewer or no such domains. This change in the haemoglobin mix is similar to the response to hypoxia in *Daphnia,* which is mediated through the transcription factor hypoxia-inducible factor 1, and ultimately the mTOR signalling pathway. This is the first report of a role for haemoglobin in the response to CR. We also observed high absolute expression of superoxide dismutase (SOD) in normally fed individuals, which contrasts with observations of high SOD levels under CR in other taxa. However, key differentially expressed genes, like SOD, were not targeted by differentially expressed micro-RNAs. Whether the link between haemoglobin and CR occurs in other organisms, or is related to the aquatic lifestyle, remains to be tested. It suggests that one response to CR may be to simply transport less oxygen and lower respiration.

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Twenty-seven-year time trends in dementia incidence in Europe and the United States

The Alzheimer Cohorts Consortium

Objective To determine changes in the incidence of dementia between 1988 and 2015.

Methods This analysis was performed in aggregated data from individuals >65 years of age in 7 population-based cohort studies in the United States and Europe from the Alzheimer Cohort Consortium. First, we calculated age- and sex-specific incidence rates for all-cause dementia, and then defined nonoverlapping 5-year epochs within each study to determine trends in incidence. Estimates of change per 10-year interval were pooled and results are presented combined and stratified by sex.

Results Of 49,202 individuals, 4,253 (8.6%) developed dementia. The incidence rate of dementia increased with age, similarly for women and men, ranging from about 4 per 1,000 person-years in individuals aged 65–69 years to 65 per 1,000 person-years for those aged 85–89 years. The incidence rate of dementia declined by 13% per calendar decade (95% confidence interval [CI], 7%–19%), consistently across studies, and somewhat more pronouncedly in men than in women (24% [95% CI 14%–32%] vs 8% [0%–15%]).

Conclusion The incidence rate of dementia in Europe and North America has declined by 13% per decade over the past 25 years, consistently across studies. Incidence is similar for men and women, although declines were somewhat more profound in men. These observations call for sustained efforts to finding the causes for this decline, as well as determining their validity in geographically and ethnically diverse populations.

Changes in the intracellular microenvironment in the aging human brain

Normal brain aging is associated with changes occurring at all levels. This study investigates age-related differences in the brain intracellular microenvironment by comparing the apparent diffusion coefficients (ADC) and apparent transverse relaxation time constants (T_2) of 5 neurochemicals (i.e., total N-acetyl-aspartate, total creatine, total choline, glutamate, and myo-inositol) between young and older adults. Thirty-two young healthy adults (18-22 years) and 26 older healthy adults (70-83 years) were recruited. Three brain regions were studied at 3 T: prefrontal, posterior cingulate and occipital cortices. ADC and T_2 were measured using stimulated echo acquisition mode and localization by adiabatic selective refocusing sequences, respectively. This study shows that the diffusivities of several neurochemicals are higher in older than in younger adults. In contrast, shorter apparent T_2 values for several metabolites were measured in older adults. Age-related difference in ADC and apparent T_2 of metabolites seem to be region-specific. Furthermore, this study shows that it is feasible to observe age-related differences in the cellular microenvironment of neurochemicals in the normal aging brain.

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A 25-y longitudinal dolphin cohort supports that long-lived individuals in same environment exhibit variation in aging rates

Stephanie Venn-Watson, Eric D. Jensen, and Nicholas J. Schork

While it is believed that humans age at different rates, a lack of robust longitudinal human studies using consensus biomarkers meant to capture aging rates has hindered an understanding of the degree to which individuals vary in their rates of aging. Because bottlenose dolphins are long-lived mammals that develop comorbidities of aging similar to humans, we analyzed data from a well-controlled, 25-y longitudinal cohort of 144 US Navy dolphins housed in the same oceanic environment. Our analysis focused on 44 clinically relevant hematologic and clinical chemistry measures recorded during routine blood draws throughout the dolphins' lifetimes. Using stepwise regression and general linear models that accommodate correlations between measures obtained on individual dolphins, we demonstrate that, in a manner similar to humans, dolphins exhibit independent and linear age-related declines in four of these measures: hemoglobin, alkaline phosphatase, platelets, and lymphocytes. Using linear regressions and analyses of covariance with post hoc Tukey–Kramer tests to compare slopes (i.e., linear age-related rates) of our four aging rate biomarkers among 34 individual dolphins aging from 10 y to up to 40 y old, we could identify slow and accelerated agers and differentiate subgroups that were more or less likely to develop anemia and lymphopenia. This study successfully documents aging rate differences over the lifetime of long-lived individuals in a controlled environment. Our study suggests that nonenvironmental factors influencing aging rate biomarkers, including declining hemoglobin and anemia, may be targeted to delay the effects of aging in a compelling model of human biology.

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Cyclodextrin polymer improves atherosclerosis therapy and reduces ototoxicity

Recently, cyclodextrin (CD) has shown the potential for effective treatment of atherosclerotic plaques in mice by solubilizing plaque cholesterol. While promising as a new therapy for atherosclerosis, poor pharmacokinetics and ototoxicity of CD pose a therapeutic challenge. Thus far, however, there has been no attempts to overcome such limitations. Here, we showed that cyclodextrin polymer (CDP) with a diameter of ~ 10 nm exhibits outstanding pharmacokinetics and plaque targeting efficacy compared to a monomeric CD. Furthermore, we found out that CDP does not induce plasma membrane disruption as opposed to CD, which eliminated cytotoxicity and hemolytic activity of CD. In a mouse model of atherosclerosis, subcutaneous injections of beta-cyclodextrin polymer (βCDP) significantly inhibited plaque growth compared to monomeric hydroxypropyl-beta-cyclodextrin (HPβCD) at the same dose (1 g/kg). More importantly, βCDP did not induce significant ototoxicity at a high-dose (8 g/kg) where HPβCD reduced the outer hair cell content by 36%. These findings suggest that the polymerization of CD can overcome major limitations of CD therapy for treatment of atherosclerosis.

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Dihydroxyacetone phosphate signals glucose availability to mTORC1

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The mechanistic target of rapamycin complex 1 (mTORC1) kinase regulates cell growth by setting the balance between anabolic and catabolic processes. To be active, mTORC1 requires the environmental presence of amino acids and glucose. While a mechanistic understanding of amino acid sensing by mTORC1 is emerging, how glucose activates mTORC1 remains mysterious. Here, we used metabolically engineered human cells lacking the canonical energy sensor AMP-activated protein kinase to identify glucose-derived metabolites required to activate mTORC1 independent of energetic stress. We show that mTORC1 senses a metabolite downstream of the aldolase and upstream of the GAPDH-catalysed steps of glycolysis and pinpoint dihydroxyacetone phosphate (DHAP) as the key molecule. In cells expressing a triose kinase, the synthesis of DHAP from DHA is sufficient to activate mTORC1 even in the absence of glucose. DHAP is a precursor for lipid synthesis, a process under the control of mTORC1, which provides a potential rationale for the sensing of DHAP by mTORC1.

C. elegans aging research

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Quantification of Insoluble Protein Aggregation in Caenorhabditis elegans during Aging with a Novel Data-Independent Acquisition Workflow

We and others have shown that the aging process results in a proteome-wide accumulation of insoluble proteins. Knocking down genes encoding the insoluble proteins over 40% of the time results in an extension of the lifespan in C. elegans, suggesting that many of these proteins are key determinants of the aging process. Isolation and quantitative identification of these insoluble proteins are crucial to understand key biological processes that occur during aging. Here, we present a modified and improved protocol that details how to extract and isolate the SDS-insoluble proteins (insolublome) from C. elegans more efficiently to streamline mass spectrometric workflows via a novel label-free quantitative proteomics analysis. This improved protocol utilizes a highly efficient sonicator for worm lysis that greatly increases efficiency for protein extraction and allows us to use significantly less starting material (approximately 3,000 worms) than in previous protocols (typically using at least 40,000 worms). Subsequent quantitative proteomic analysis of the insolublome was performed using data-dependent acquisition (DDA) for protein discovery and identification and data-independent acquisition (DIA) for comprehensive and more accurate protein quantification. Bioinformatic analysis of quantified proteins provides potential candidates that can be easily followed up with other molecular methods in C. elegans. With this workflow, we routinely identify more than 1000 proteins and quantify more than 500 proteins. This new protocol enables efficient compound screening with C. elegans. Here, we validated and applied this improved protocol to wild-type C. elegans N2-Bristol strain and confirmed that aged day-10 N2 worms showed greater accumulation of the insolublome than day-2 young worms.

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Multidimensional phenotyping predicts lifespan and quantifies health in *Caenorhabditis elegans*

Céline N. Martineau, André E. X. Brown, Patrick Laurent

Ageing affects a wide range of phenotypes at all scales, but an objective measure of ageing remains challenging, even in simple model organisms. To measure the ageing process, we characterized the sequence of alterations of multiple phenotypes at organismal scale. Hundreds of morphological, postural, and behavioral features were extracted from high-resolution videos. Out of the 1019 features extracted, 896 are ageing biomarkers, defined as those that show a significant correlation with relative age (age divided by lifespan). We used support vector regression to predict age, remaining life and lifespan of individual *C. elegans*. The quality of these predictions (age $R^2 = 0.79$; remaining life $R^2 = 0.77$; lifespan $R^2 = 0.72$) increased with the number of features added to the model, supporting the use of multiple features to quantify ageing. We quantified the rate of ageing as how quickly animals moved through a phenotypic space; we quantified health decline as the slope of the declining predicted remaining life. In both ageing dimensions, we found that short lived-animals aged faster than long-lived animals. In our conditions, for isogenic wild-type worms, the health decline of the individuals was scaled to their lifespan without significant deviation from the average for short- or long-lived animals.

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Gluconeogenesis and PEPCK are critical components of healthy aging and dietary restriction life extension

Brian Onken, Natallia Kalinava, Monica Driscoll

High glucose diets are unhealthy, although the mechanisms by which elevated glucose is harmful to whole animal physiology are not well understood. In *Caenorhabditis elegans*, high glucose shortens lifespan, while chemically inflicted glucose restriction promotes longevity. We investigated the impact of glucose metabolism on aging quality (maintained locomotory capacity and median lifespan) and found that, in addition to shortening lifespan, excess glucose negatively impacts locomotory healthspan. Conversely, disrupting glucose utilization by knockdown of glycolysis-specific genes results in large mid-age physical improvements via a mechanism that requires the FOXO transcription factor DAF-16. Adult locomotory capacity is extended by glycolysis disruption, but maximum lifespan is not, indicating that limiting glycolysis can increase the proportion of life spent in mobility health. We also considered the largely ignored role of glucose biosynthesis (gluconeogenesis) in adult health. Directed perturbations of gluconeogenic genes that specify single direction enzymatic reactions for glucose synthesis decrease locomotory healthspan, suggesting that gluconeogenesis is needed for healthy aging. Consistent with this idea, overexpression of the central gluconeogenic gene *pck-2* (encoding PEPCK) increases health measures via a mechanism that requires DAF-16 to promote *pck-2* expression in specific intestinal cells. Dietary restriction also features DAF-16-dependent *pck-2* expression in the intestine, and the healthspan benefits conferred by dietary restriction require *pck-2*. Together, our results describe a new paradigm in which nutritional signals engage gluconeogenesis to influence aging quality via DAF-16. These data underscore the idea that promotion of gluconeogenesis might be an unappreciated goal for healthy aging and could constitute a novel target for pharmacological interventions that counter high glucose consequences, including diabetes.

VRK-1 extends life span by activation of AMPK via phosphorylation

Vaccinia virus–related kinase (VRK) is an evolutionarily conserved nuclear protein kinase. VRK-1, the single *Caenorhabditis elegans* VRK ortholog, functions in cell division and germline proliferation. However, the role of VRK-1 in postmitotic cells and adult life span remains unknown. Here, we show that VRK-1 increases organismal longevity by activating the cellular energy sensor, AMP-activated protein kinase (AMPK), via direct phosphorylation. We found that overexpression of *vrk-1* in the soma of adult *C. elegans* increased life span and, conversely, inhibition of *vrk-1* decreased life span. In addition, *vrk-1* was required for longevity conferred by mutations that inhibit *C. elegans* mitochondrial respiration, which requires AMPK. VRK-1 directly phosphorylated and up-regulated AMPK in both *C. elegans* and cultured human cells. Thus, our data show that the somatic nuclear kinase, VRK-1, promotes longevity through AMPK activation, and this function appears to be conserved between *C. elegans* and humans.

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eIF2B extends lifespan through inhibition of the integrated stress response

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Abstract

Protein homeostasis is modulated by stress response pathways and its deficiency is a hallmark of aging. The integrated stress response (ISR) is a conserved stress-signaling pathway that tunes mRNA translation via phosphorylation of the translation initiation factor eIF2. ISR activation and translation initiation are finely balanced by eIF2 kinases and by the eIF2 guanine nucleotide exchange factor eIF2B. However, the role of the ISR during aging remains unexplored. Using a genomic screen in *Caenorhabditis elegans*, we discovered a role of eIF2B and the eIF2 kinases in longevity. By limiting the ISR, these mutations enhanced protein homeostasis and increased lifespan. Consistently, full ISR inhibition using phosphorylation-defective eIF2α or pharmacological ISR inhibition prolonged lifespan. Lifespan extension through ISR inhibition occurred without changes in overall protein synthesis, and depended on enhanced translational efficiency of the kinase KIN-35. Evidently, lifespan is limited by the ISR and its inhibition may provide an intervention in aging.

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Reduced insulin signalling in adulthood protects soma and germline under mutation accumulation

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Abstract

Dominant theory maintains that organisms age due to resource allocation trade-offs between the immortal germline and the disposable soma. Strikingly, adulthood-only downregulation of insulin signalling, an evolutionarily conserved pathway regulating resource allocation between reproduction and soma, increases lifespan and offspring fitness without fecundity cost in the nematode, *Caenorhabditis elegans*. Nevertheless, theory suggests that reduced germline maintenance can be a hidden cost of lifespan extension. We ran a mutation accumulation (MA) experiment and downregulated insulin signalling in half of the 400 MA lines by silencing *daf-2* gene expression using RNA interference (RNAi) across 40 generations. Adulthood-only *daf-2* RNAi reduced extinction of MA lines both under UV-induced and spontaneous mutation accumulation. Fitness of the surviving UV-induced MA lines was higher under *daf-2* RNAi. Our results suggest that reduced insulin signalling protects the soma and the germline and imply that suboptimal gene expression in adulthood is a major driver of organismal ageing.

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Organismal Protein Homeostasis Mechanisms

Thorsten Hoppe and Ehud Cohen

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Abstract

Sustaining a healthy proteome is a lifelong challenge for each individual cell of an organism. However, protein homeostasis or proteostasis is constantly jeopardized since damaged proteins accumulate under proteotoxic stress that originates from ever-changing metabolic, environmental, and pathological conditions. Proteostasis is achieved via a conserved network of quality control pathways that orchestrate the biogenesis of correctly folded proteins, prevent proteins from misfolding, and remove potentially harmful proteins by selective degradation. Nevertheless, the proteostasis network has a limited capacity and its collapse deteriorates cellular functionality and organismal viability, causing metabolic, oncological, or neurodegenerative disorders. While cell-autonomous quality control mechanisms have been described intensely, recent work on *Caenorhabditis elegans* has demonstrated the systemic coordination of proteostasis between distinct tissues of an organism. These findings indicate the existence of intricately balanced proteostasis networks important for integration and maintenance of the organismal proteome, opening a new door to define novel therapeutic targets for protein aggregation diseases. Here, we provide an overview of individual protein quality control pathways and the systemic coordination between central proteostatic nodes. We further provide insights into the dynamic regulation of cellular and organismal proteostasis mechanisms that integrate environmental and metabolic changes. The use of *C. elegans* as a model has pioneered our understanding of conserved quality control mechanisms important to safeguard the organismal proteome in health and disease.

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The heat shock transcription factor HSF-1 protects *Caenorhabditis elegans* from peroxide stress

Cells induce conserved defense mechanisms that protect them from oxidative stress. How these defenses are regulated in multicellular organisms is incompletely understood. Here, we show that the heat shock transcription factor HSF-1 protects the nematode *Caenorhabditis elegans* from the oxidative stress caused by environmental peroxide. In response to a heat shock or a mild temperature increase, HSF-1 protects the nematodes from subsequent peroxide stress in a manner that depends on HSF-1's transactivation domain. At constant temperature, HSF-1 protects the nematodes from peroxide stress independently of its transactivation domain, likely by inducing the expression of *asp-4/cathepsin* and *dapk-1/dapk*. Thus, two distinct HSF-1-dependent processes protect C. *elegans* from peroxide stress.

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A Mitochondrial Stress-Specific Form of HSF1 Protects against Age-Related Proteostasis Collapse

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Affiliations + expand

PMID: 32735771 DOI: 10.1016/j.devcel.2020.06.038

Abstract

The loss of protein homeostasis (proteostasis) is a primary driver of age-related tissue dysfunction. Recent studies have revealed that the failure of proteostasis with age is triggered by developmental and reproductive cues that repress the activity of proteostasis-related pathways in early adulthood. In Caenorhabditis elegans, reduced mitochondrial electron transport chain (ETC) function during development can override signals that promote proteostasis collapse in aged tissues. However, it is unclear precisely how these beneficial effects are mediated. Here, we reveal that in response to ETC impairment, the PP2A complex generates a dephosphorylated, mitochondrial stress-specific variant of the transcription factor HSF-1. This results in the selective induction of small heat shock proteins in adulthood, thereby protecting against age-related proteostasis collapse. We propose that mitochondrial signals early in life can protect the aging cytosolic proteome by tailoring HSF-1 activity to preferentially drive the expression of non-ATP-dependent chaperones.

REVIEWS/COMMENTS/ METHODS/EDITORIALS

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Feature » Health and Ageing

Geroscience's coming of age

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The search for a fountain of youth endures across cultures. But the time is coming when we treat ageing as a disease, not an inevitability, reports **Bob Roehr**

The lifespan of worms can be increased 10-fold through a single mutation to the insulin signaling pathway. The lifespan of a mouse can be upped by 50%. As for humans, however, "There is still this notion among physicians and the public in general that ageing is an inevitable universal process, that there's not much you can do about it," says Joao Pedro de Magalhães, a professor at the Institute of Ageing and Chronic Disease at the University of Liverpool, UK. "And that's not true."

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You Have Come A Long Way Baby: Five Decades of Research on the Biology of Aging from the Perspective of a Researcher Studying Aging.

Arlan Richardson, PhD

Abstract

In the 46 years since the establishment of the National Institute on Aging, the progress on our understanding of the biology of aging has been phenomenal. We have gone from an area of research that was primarily descriptive to the point that we now have genetic and pharmacological interventions that can increase lifespan and slow aging in invertebrates and mice. Unfortunately, we have been slow to move these discoveries from laboratory animals to humans and improve the health of the elderly. This article describes some of the seminal discoveries in aging that have led to the biology of aging becoming one of the hottest areas of research, resulting in Science recognizing discoveries in aging as one of the top ten scientific breakthroughs in 2009 and 2011. For the first time in human history, we are now in a position to begin testing potential aging interventions in humans.

Health and Immortality

Is maintaining good health potentially compatible with a significant or radical life extension? Historically, these phenomena have often been seen as conflicting. Their potential principal incompatibility has often been derived from either health (functional capacity) or lifespan being understood as finite or limited values. The various concepts of limitations to the lifespan or health quantity are surveyed in this work in their historical development, with reference to several dominant theories of aging and mortality. The incompleteness and ambiguities of the limitation theories are demonstrated. Thus, even when proposing limits to the lifespan or healthspan, these limits have often been seen, even by the same authors, as flexible and modifiable. The exact conditions under which lifespan and healthspan "limitations" end and the "possibilities" of their enhancement begin have remained uncertain in the absence of a reliable quantitative formal theory of aging and mortality. An alternative "life-extensionist" view assumes the potential replenishment of any vital resources expended, and thus presumes no inherent natural limitations to either the lifespan or health quantity (functional capacity). The validity of either of those views may be tested in the future with the development of new medical technologies and a better theoretical understanding of health, aging and mortality.

Dementia prevention, intervention, and care: 2020 report of the *Lancet* Commission

The number of older people, including those living with dementia, is rising, as younger age mortality declines. However, the age-specific incidence of dementia has fallen in many countries, probably because of improvements in education, nutrition, health care, and lifestyle changes. Overall, a growing body of evidence supports the nine potentially modifiable risk factors for dementia modelled by the 2017 *Lancet* Commission on dementia prevention, intervention, and care: less education, hypertension, hearing impairment, smoking, obesity, depression, physical inactivity, diabetes, and low social contact. We now add three more risk factors for dementia with newer, convincing evidence. These factors are excessive alcohol consumption, traumatic brain injury, and air pollution. We have completed new reviews and meta-analyses and incorporated these into an updated 12 risk factor life-course model of dementia prevention. Together the 12 modifiable risk factors account for around 40% of worldwide dementias, which consequently could theoretically be prevented or delayed. The potential for prevention is high and might be higher in low-income and middle-income countries (LMIC) where more dementias occur.

Our new life-course model and evidence synthesis has paramount worldwide policy implications. It is never too early and never too late in the life course for dementia prevention. Early-life (younger than 45 years) risks, such as less education, affect cognitive reserve; midlife (45–65 years), and later-life (older than 65 years) risk factors influence reserve and triggering of neuropathological developments. Culture, poverty, and inequality are key drivers of the need for change. Individuals who are most deprived need these changes the most and will derive the highest benefit.

Animal models of sarcopenia

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Free article

Abstract

Sarcopenia is the age-related decline in muscle mass and function without any underlying disease. The exact molecular mechanisms responsible for this pathology remain unknown. The use of model organisms, such as mice, rats, flies, and worms, has advanced the field of sarcopenia research by identifying therapeutic strategies and genetic mutations that result in improved muscle mass and function of elderly animals. This review discusses molecular and therapeutic discoveries made using these model organisms and how these animals can be further utilized to better understand sarcopenia pathogenesis. In rodents, flies, and worms, dietary restriction improves muscle performance in old animals. In rodents and worms, exercise and a number of naturally occurring compounds alleviate sarcopenia. Reduction in the insulin/IGF1 receptor pathway, well known to promote longevity, improves sarcopenia in worms and flies. Mitochondrial dysfunction may contribute to the pathogenesis of sarcopenia: In rodents, there is age-dependent reduction in mitochondrial mass and a change in morphology; in nematodes, there is age-dependent fragmentation of mitochondria that precedes sarcomeric disorganization. In Drosophila and rats, components of the 26S proteasome are elevated in aged muscle. An advantage of the worm and fly models is that these organisms lack muscle stem cells, and thus processes that promote the maintenance of already assembled muscle, can be identified without the confounding influence of muscle regeneration. Zebrafish are an up and coming model of sarcopenia for future consideration. A better understanding of the molecular changes behind sarcopenia will help researchers develop better therapies to improve the muscle health of elderly individuals.

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Inflammaging, hormesis and the rationale for anti-aging strategies

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PMID: 32814129 DOI: 10.1016/j.arr.2020.101142

Abstract

We propose in this review that hormesis, a concept profoundly and systematically addressed by Mark Mattson, has to be considered a sort of comprehensive "contact point" capable of unifying several conceptualizations of the aging process, including those focused on the stress response, oxidative stress and chronic inflammation/inflammaging. A major strength of hormesis and inflammaging is that they have a strong evolutionary basis. Moreover, both hormesis and inflammaging frame the aging process within a lifelong perspective of adaptation to different types of stresses. Such adaptation perspective also suggests that the aging process is malleable, and predicts that effective anti-aging strategies should mimic what evolution did in the course of million years and that we have to learn how to exploit the great potential inherent in the hormetic/inflammatory responses. To this regard, new topics such as the production of mitokines to cope with mitochondrial dysfunction are emerging as possible anti-aging target. This approach opens theoretically the door to the possibility of modulating the individual aging rate and trajectory by adopting the most effective scientifically-based lifestyle regarding fundamentally nutrition and physical activity. In this scenario Mark Mattson's lesson and personal example will permanently enlighten the aging field and the quest for a healthy aging and longevity.

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A Senescence-Centric View of Aging: Implications for Longevity and Disease

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Cellular senescence is a state of stable cell cycle arrest associated with macromolecular alterations and secretion of proinflammatory cytokines and molecules. From their initial discovery in the 1960s, senescent cells have been hypothesized as potential contributors to the age-associated loss of regenerative potential. Here, we discuss recent evidence that implicates cellular senescence as a central regulatory mechanism of the aging process. We provide a comprehensive overview of age-associated pathologies in which cellular senescence has been implicated. We describe mechanisms by which senescent cells drive aging and diseases, and we discuss updates on exploiting these mechanisms as therapeutic targets. Finally, we critically analyze the use of senotherapeutics and their translation to the clinic, highlighting limitations and suggesting ideas for future applications and developments.

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Exercise and cardiac health: physiological and molecular insights

Jose B. N. Moreira[1], Martin Wohlwend[1] and Ulrik Wisløff[1,2] ✉

The cardiac benefits of exercise have been recognized for centuries. Studies have undisputedly shown that regular exercise is beneficial for the cardiovascular system in young, old, healthy and diseased populations. For these reasons, physical activity has been recommended worldwide for cardiovascular disease prevention and treatment. Although the benefits of exercise are clear, understanding of the molecular triggers that orchestrate these effects remains incomplete and has been a topic of intense research in recent years. Here, we provide a comprehensive review of the cardiac effects of physical activity, beginning with a brief history of exercise in cardiovascular medicine and then discussing seminal work on the physiological effects of exercise in healthy, diseased and aged hearts. Later, we revisit pioneering work on the molecular mechanisms underlying the cardiac benefits of exercise, and we conclude with our view on the translational potential of this knowledge as a powerful platform for cardiovascular disease drug discovery.

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Anti-Aging Effect of Metformin: A Molecular and Therapeutical Perspective

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Abstract

Aging is a time-dependent inevitable process, in which cellular homeostasis is affected, which has an impact on tissue function. This represents a risk factor for the development of numerous non-transmissible diseases. In consequence, the scientific community continues to search for therapeutic measures capable of improving quality of life and delaying cellular aging. At the center of this research is metformin, a widely used drug in Type 2 Diabetes Mellitus treatment that has a reduced adverse effects profile. Furthermore, there is evidence that this drug has beneficial health effects that go beyond its anti-hyperglycemic properties. Among these effects, its geronto-protection capability stands out. There is growing evidence that points out to an increased life expectancy as well as quality of life in model organisms treated with metformin. Therefore, there is an abundance of research centered on elucidating the mechanism through which metformin has its anti-aging effects. Among these, the AMPK, mTORC1, SIRT1, FOXO, NF.kB, and DICER1 pathways can be mentioned. Furthermore, studies have highlighted the possibility of a role for gut microbiome in these processes. The next step is the design of clinical essays that have as a goal evaluating the efficacy and safety of metformin as an anti-aging drug in humans to create a paradigm in the medical horizon. The question being if metformin is in fact the new anti-aging therapy in humans?

OTHER RESEARCH & REVIEWS

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HEALTHY LIFE EXTENSION SOCIETY

Multichannel Electrocardiograms Obtained by a Smartwatch for the Diagnosis of ST-Segment Changes

Importance Acute coronary syndromes are the leading cause of death worldwide and the leading cause of disease burden in high-income countries. Quick and accurate diagnosis of acute coronary syndromes is essential to avoid fatal events, for timely intervention, and to improve the prognosis.

Objective To prospectively investigate the feasibility and accuracy of a smartwatch in recording multiple electrocardiographic (ECG) leads and detecting ST-segment changes associated with acute coronary syndromes compared with a standard 12-lead ECG.

Design, Setting, and Participants A commercially available smartwatch was used in 100 participants to obtain multiple-channel ECGs. The study was conducted from April 19, 2019, to January 23, 2020. Fifty-four patients with ST elevation myocardial infarction, 27 patients with non-ST elevation myocardial infarction, and 19 healthy individuals were included in the study. The watch was placed in different body positions to obtain 9 bipolar ECG tracings (corresponding to Einthoven leads I, II, and III and precordial leads V1-V6) that were compared with a simultaneous standard 12-lead ECG.

Main Outcomes and Measures The concordance among the results of the smartwatch and standard ECG recordings was assessed using the Cohen κ coefficient and Bland-Altman analysis.

Results Of the 100 participants in the study, 67 were men (67%); mean (SD) age was 61 (16) years. Agreement was found between the smartwatch and standard ECG for the identification of a normal ECG (Cohen κ coefficient, 0.90; 95% CI, 0.78-1.00), ST-segment elevation changes (Cohen κ coefficient, 0.88; 95% CI, 0.78-0.97), and non–ST-segment elevation changes (Cohen κ coefficient, 0.85; 95% CI, 0.74-0.96). In addition, the Bland-Altman analysis demonstrated agreement between the smartwatch and standard ECG to detect the amplitude of ST-segment changes (bias, −0.003; SD, 0.18; lower limit, −0.36; and upper limit, 0.36). Use of the smartwatch ECG for the diagnosis of normal ECG showed a sensitivity of 84% (95% CI, 60%-97%) and specificity of 100% (95% CI, 95%-100%); for ST elevation, sensitivity was 93% (95% CI, 82%-99%) and specificity was 95% (95% CI, 85%-99%); and for NSTE ECG alterations, sensitivity was 94% (95% CI, 81%-99%) and specificity was 92% (95% CI, 83%-97%).

Conclusions and Relevance The findings of this study suggest agreement between the multichannel smartwatch ECG and standard ECG for the identification of ST-segment changes in patients with acute coronary syndromes.

ESC: Eli Lilly, Boehringer's Jardiance slices CV events by 25% in Farxiga-matching heart failure trial

AstraZeneca put the rest of the SGLT2 inhibitor class on notice when its Farxiga scored an FDA heart failure nod in patients with or without diabetes. One of its competitors, Eli Lilly and Boehringer Ingelheim's Jardiance, is fast on Farxiga's heels, though, and it's ready to bring its pivotal trial win in front of physicians.

Jardiance, added to standard of care therapy, sliced the risk of cardiovascular hospitalizations or death by 25% over placebo in heart failure patients with or without Type 2 diabetes, according to late-breaking science set to be presented Saturday at the European Society of Cardiology virtual annual meeting.

The full data from the phase 3 Emperor-Reduced trial comes just weeks after the drugmakers declared a top-line win in their pursuit of SGLT2 rival Farxiga, which scored the class' first FDA approval in that indication back in May.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Risk of 16 cancers across the full glycemic spectrum: a population-based cohort study using the UK Biobank

Introduction: Diabetes is observed to increase cancer risk, leading to hypothesized direct effects of either hyperglycemia or medication. We investigated associations between glycosylated hemoglobin (HbA1c) across the whole glycemic spectrum and incidence of 16 cancers in a population sample with comprehensive adjustment for risk factors and medication.

Research design and methods: Linked data from the UK Biobank and UK cancer registry for all individuals with baseline HbA1c and no history of cancer at enrollment were used. Incident cancer was based on International Classification of Diseases - 10th Edition diagnostic codes. Age-standardized incidence rates were estimated by HbA1c category. Associations between HbA1c, modeled as a restricted cubic spline, and cancer risk were estimated using Cox proportional hazards models.

Results: Among 378 253 individuals with average follow-up of 7.1 years, 21 172 incident cancers occurred. While incidence for many of the 16 cancers was associated with hyperglycemia in crude analyses, these associations disappeared after multivariable adjustment, except for pancreatic cancer (HR 1.55, 95% CI 1.22 to 1.98 for 55 vs 35 mmol/mol), and a novel finding of an inverse association between HbA1c and premenopausal breast cancer (HR 1.27, 95% CI 1.00 to 1.60 for 25 vs 35 mmol/mol; HR 0.71, 95% CI 0.54 to 0.94 for 45 vs 35 mmol/mol), not observed for postmenopausal breast cancer. Adjustment for diabetes medications had no appreciable impact on HRs for cancer.

Conclusions: Apart from pancreatic cancer, we did not demonstrate any independent positive association between HbA1c and cancer risk. These findings suggest that the potential for a cancer-inducing, direct effect of hyperglycemia may be misplaced.

Keywords: cohort studies; epidemiology; glycated hemoglobin A; hyperglycemia.