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Scientific News
4th of July 2021
Sven Bulterijs

Business/Conferences/ General news

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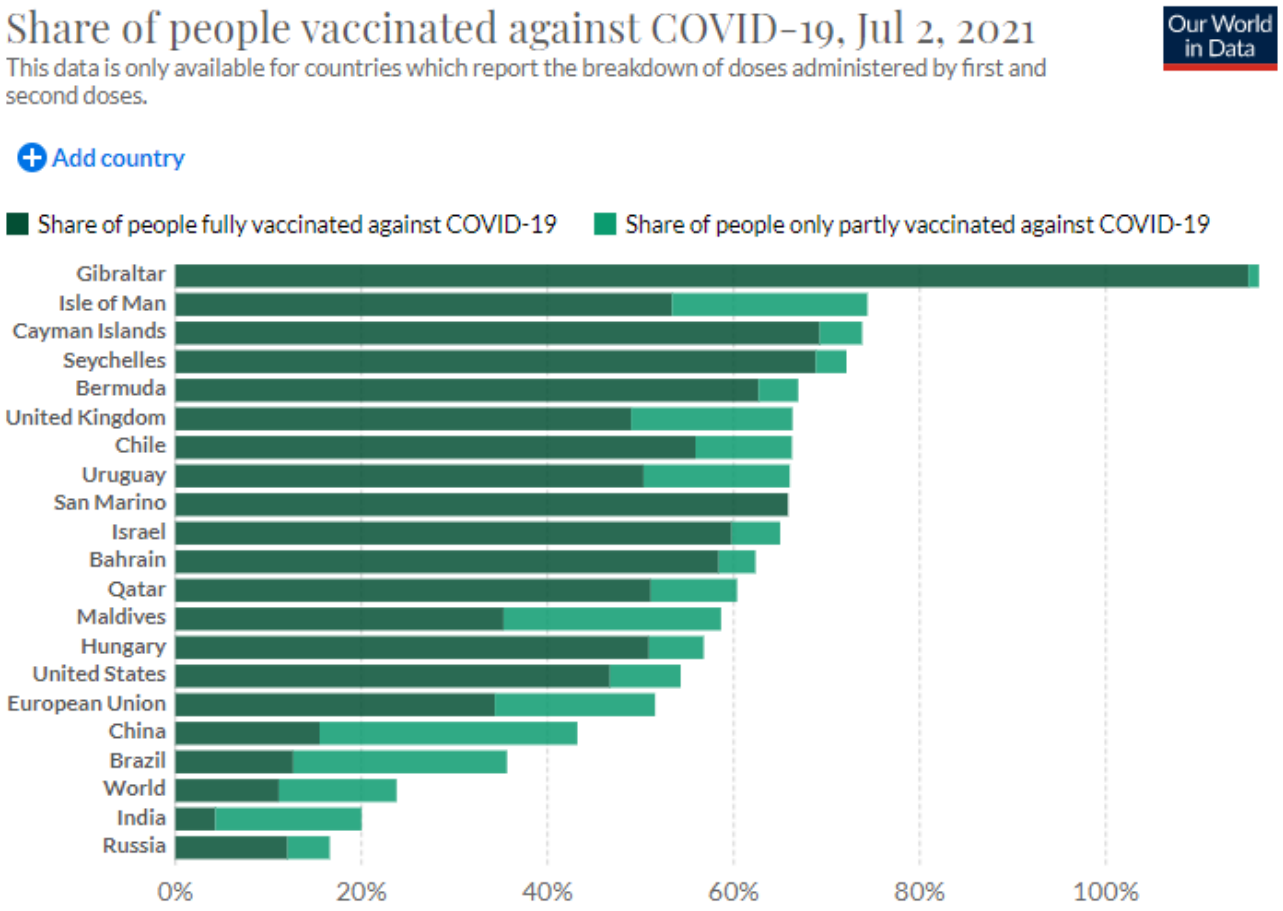
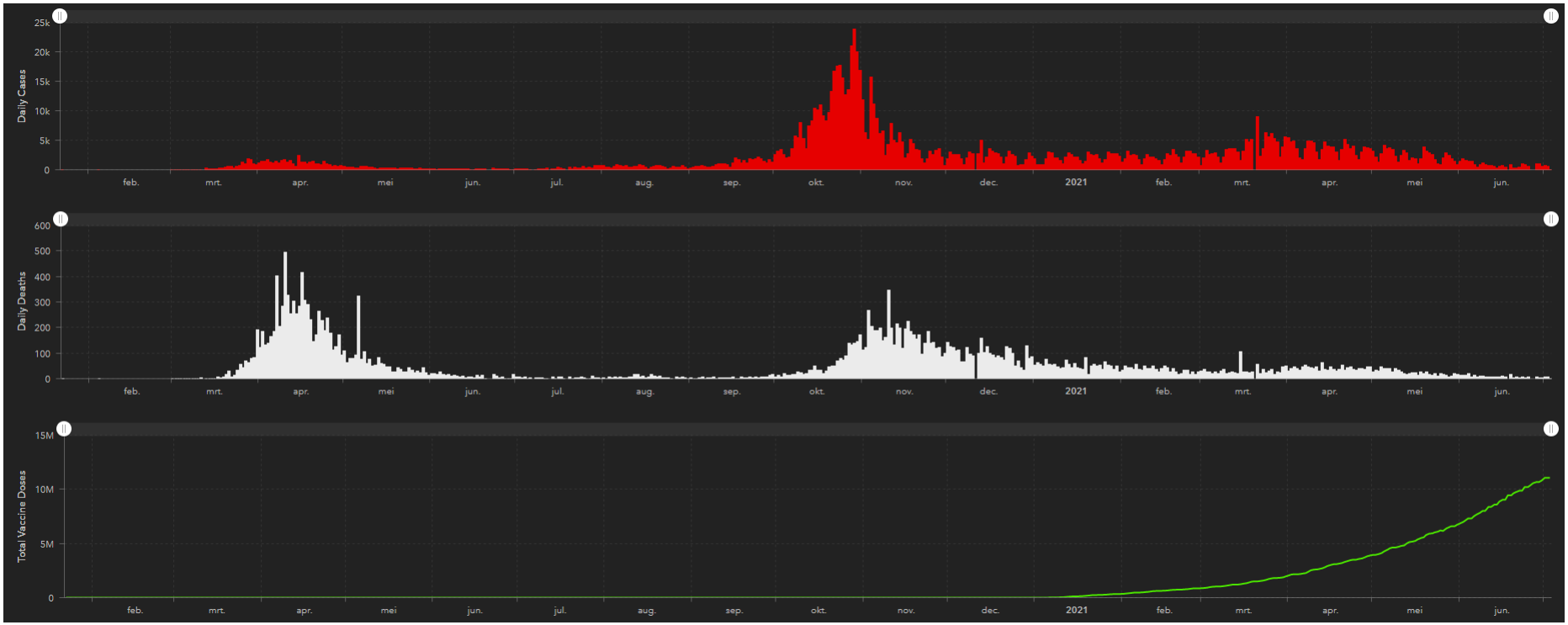
Cases	Deaths	Vaccine Doses Administered
183.505.842	3.971.956	3.169.882.522



Belgium



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Breathing, speaking, coughing or sneezing: What drives transmission of SARS-CoV-2?

V. Stadnytskyi, P. Anfinrud ✉, A. Bax ✉

First published: 08 June 2021 | https://doi.org/10.1111/joim.13326

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Abstract

The SARS-CoV-2 virus is highly contagious, as demonstrated by numerous well-documented superspreading events. The infection commonly starts in the upper respiratory tract (URT) but can migrate to the lower respiratory tract (LRT) and other organs, often with severe consequences. Whereas LRT infection can lead to shedding of virus via breath and cough droplets, URT infection enables shedding via abundant speech droplets. Their viral load can be high in carriers with mild or no symptoms, an observation linked to the abundance of SARS-CoV-2-susceptible cells in the oral cavity epithelium. Expelled droplets rapidly lose water through evaporation, with the smaller ones transforming into long-lived aerosol. Although the largest speech droplets can carry more virions, they are few in number, fall to the ground rapidly and therefore play a relatively minor role in transmission. Of more concern is small speech aerosol, which can descend deep into the LRT and cause severe disease. However, since their total volume is small, the amount of virus they carry is low. Nevertheless, in closed environments with inadequate ventilation, they can accumulate, which elevates the risk of direct LRT infection. Of most concern is the large fraction of speech aerosol that is intermediate-sized because it remains suspended in air for minutes and can be transported over considerable distances by convective air currents. The abundance of this speech-generated aerosol, combined with its high viral load in pre- and asymptomatic individuals, strongly implicates airborne transmission of SARS-CoV-2 through speech as the primary contributor to its rapid spread.

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Mass mask-wearing notably reduces COVID-19 transmission

Mask-wearing has been a controversial measure to control the COVID-19 pandemic. While masks are known to substantially reduce disease transmission in healthcare settings [1–3], studies in community settings report inconsistent results [4–6].

Investigating the inconsistency within epidemiological studies, we find that a commonly used proxy, government mask mandates, does not correlate with large increases in mask-wearing in our window of analysis. We thus analyse the effect of mask-wearing on transmission instead, drawing on several datasets covering 92 regions on 6 continents, including the largest survey of individual-level wearing behaviour (n=20 million) [7]. Using a hierarchical Bayesian model, we estimate the effect of both mask-wearing and mask-mandates on transmission by linking wearing levels (or mandates) to reported cases in each region, adjusting for mobility and non-pharmaceutical interventions.

We assess the robustness of our results in 123 experiments spanning 22 sensitivity analyses. Across these analyses, we find that an entire population wearing masks in public leads to a median reduction in the reproduction number *R* of 25.8%, with 95% of the medians between 22.2% and 30.9%. In our window of analysis, the median reduction in *R* associated with the wearing level observed in each region was 20.4% [2.0%, 23.3%][1]. We do not find evidence that mandating mask-wearing reduces transmission. Our results suggest that mask-wearing is strongly affected by factors other than mandates.

We establish the effectiveness of mass mask-wearing, and highlight that wearing data, not mandate data, are necessary to infer this effect.

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Impact of SARS-CoV-2 variants on the total CD4$^+$ and CD8$^+$ T cell reactivity in infected or vaccinated individuals

AUTHORS

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SUMMARY

The emergence of SARS-CoV-2 variants with evidence of antibody escape highlight the importance of addressing whether the total CD4$^+$ and CD8$^+$ T cell recognition is also affected. Here, we compare SARS-CoV-2-specific CD4$^+$ and CD8$^+$ T cells against the B.1.1.7, B.1.351, P.1, and CAL.20C lineages in COVID-19 convalescents and in recipients of the Moderna (mRNA-1273) or Pfizer/BioNTech (BNT162b2) COVID-19 vaccines. The total reactivity against SARS-CoV-2 variants is similar in terms of magnitude and frequency of response, with decreases in the 10 to 22% range observed in some assay/VOC combinations. A total of 7% and 3% of previously identified CD4$^+$ and CD8$^+$ T cell epitopes, respectively, are impacted by mutations in the various VOCs. Thus, SARS-CoV-2 variants analyzed herein do not majorly disrupt the total SARS-CoV-2 T cell reactivity; however, the decreases observed highlight the importance for active monitoring of T cell reactivity in the context of SARS-CoV-2 evolution.

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PREPRINT

Ad26.COV2.S elicited neutralizing activity against Delta and other SARS-CoV-2 variants of concern

Mandy Jongeneelen, Krisztian Kaszas, Daniel Veldman, Jeroen Huizingh, Remko van der Vlugt, Theo Schouten, David Zuijdgeest, Taco Uil, Griet van Roey, Nuria Guimera, Marjon Navis, Rinke Bos, Mathieu le Gars, Jerald Sadoff, Leacky Muchene, Jarek Juraszek, Johannes PM Langedijk, Ronald Vogels, Jerome Custers, Hanneke Schuitemaker, Boerries Brandenburg

doi: https://doi.org/10.1101/2021.07.01.450707

Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to evolve and recently emerging variants with substitutions in the Spike protein have led to growing concerns over increased transmissibility and decreased vaccine coverage due to immune evasion. Here, sera from recipients of a single dose of our Ad26.COV2.S COVID-19 vaccine were tested for neutralizing activity against several SARS-CoV-2 variants of concern. All tested variants demonstrated susceptibility to Ad26.COV2.S-induced serum neutralization albeit mainly reduced as compared to the B.1 strain. Most pronounced reduction was observed for the B.1.351 (Beta; 3.6-fold) and P.1 (Gamma; 3.4-fold) variants that contain similar mutations in the receptor-binding domain (RBD) while only a 1.6-fold reduction was observed for the widely spreading B.1.617.2 (Delta) variant.

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July 1, 2021
4:12 PM CEST
Last Updated 3 days ago

United Kingdom

Public Health England: AstraZeneca COVID shot 94% protective against death in over 65s

2 minute read

Reuters

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Community-level evidence for SARS-CoV-2 vaccine protection of unvaccinated individuals

Oren Milman, Idan Yelin, Noga Aharony, Rachel Katz, Esma Herzel, Amir Ben-Tov, Jacob Kuint, Sivan Gazit, Gabriel Chodick, Tal Patalon ✉ & Roy Kishony ✉

Nature Medicine (2021) | Cite this article

Abstract

Mass vaccination has the potential to curb the current COVID-19 pandemic by protecting individuals who have been vaccinated against the disease and possibly lowering the likelihood of transmission to individuals who have not been vaccinated. The high effectiveness of the widely administered BNT162b vaccine from Pfizer–BioNTech in preventing not only the disease but also infection with SARS-CoV-2 suggests a potential for a population-level effect, which is critical for disease eradication. However, this putative effect is difficult to observe, especially in light of highly fluctuating spatiotemporal epidemic dynamics. Here, by analyzing vaccination records and test results collected during the rapid vaccine rollout in a large population from 177 geographically defined communities, we find that the rates of vaccination in each community are associated with a substantial later decline in infections among a cohort of individuals aged under 16 years, who are unvaccinated. On average, for each 20 percentage points of individuals who are vaccinated in a given population, the positive test fraction for the unvaccinated population decreased approximately twofold. These results provide observational evidence that vaccination not only protects individuals who have been vaccinated but also provides cross-protection to unvaccinated individuals in the community.

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Impact of vaccination on new SARS-CoV-2 infections in the United Kingdom

The effectiveness of COVID-19 vaccination in preventing new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections in the general community is still unclear. Here, we used the Office for National Statistics COVID-19 Infection Survey—a large community-based survey of individuals living in randomly selected private households across the United Kingdom—to assess the effectiveness of the BNT162b2 (Pfizer–BioNTech) and ChAdOx1 nCoV-19 (Oxford–AstraZeneca; ChAdOx1) vaccines against any new SARS-CoV-2 PCR-positive tests, split according to self-reported symptoms, cycle threshold value (<30 versus ≥30; as a surrogate for viral load) and gene positivity pattern (compatible with B.1.1.7 or not). Using 1,945,071 real-time PCR results from nose and throat swabs taken from 383,812 participants between 1 December 2020 and 8 May 2021, we found that vaccination with the ChAdOx1 or BNT162b2 vaccines already reduced SARS-CoV-2 infections ≥21 d after the first dose (61% (95% confidence interval (CI) = 54–68%) versus 66% (95% CI = 60–71%), respectively), with greater reductions observed after a second dose (79% (95% CI = 65–88%) versus 80% (95% CI = 73–85%), respectively). The largest reductions were observed for symptomatic infections and/or infections with a higher viral burden. Overall, COVID-19 vaccination reduced the number of new SARS-CoV-2 infections, with the largest benefit received after two vaccinations and against symptomatic and high viral burden infections, and with no evidence of a difference between the BNT162b2 and ChAdOx1 vaccines.

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Nasal delivery of an IgM offers broad protection from SARS-CoV-2 variants

Resistance represents a major challenge for antibody-based therapy for coronavirus disease 2019 (COVID-19)[1–4]. Here we engineered an immunoglobulin M (IgM) neutralizing antibody (IgM-14) to overcome the resistance encountered by IgG-based therapeutics. IgM-14 is >230-fold more potent than its parental IgG-14 in neutralizing the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). IgM-14 potently neutralizes the resistant virus raised by its corresponding IgG-14, the newly emerged United Kingdom B.1.1.7, Brazilian P.1, and South African B.1.351 variants of concern (VOCs), and 21 other receptor-binding domain (RBD) mutants, many of which are resistant to the IgGs that have been authorized for emergency use. Although engineering IgG into IgM enhances antibody potency in general, selection of an optimal epitope is critical for identifying the most effective IgM that can overcome resistance. One single intranasal (IN) dose of 0.044 and 0.4 mg/kg IgM-14 confers prophylactic and therapeutic efficacy against SARS-CoV-2 in mice, respectively. IgM-14, but not IgG-14, also confers potent therapeutic protection against the P.1 and B.1.351 variants. IgM-14 exhibits desirable IN pharmacokinetics and safety in rodents. Our results demonstrate that IN administration of an engineered IgM can improve efficacy, reduce resistance, and simplify the prophylactic and therapeutic treatment of COVID-19.

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Establishing the prevalence of common tissue-specific autoantibodies following severe acute respiratory syndrome coronavirus 2 infection

Coronavirus 19 (COVID-19) has been associated with both transient and persistent systemic symptoms that do not appear to be a direct consequence of viral infection. The generation of autoantibodies has been proposed as a mechanism to explain these symptoms. To understand the prevalence of autoantibodies associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, we investigated the frequency and specificity of clinically relevant autoantibodies in 84 individuals previously infected with SARS-CoV-2, suffering from COVID-19 of varying severity in both the acute and convalescent setting. These were compared with results from 32 individuals who were on the intensive therapy unit (ITU) for non-COVID reasons. We demonstrate a higher frequency of autoantibodies in the COVID-19 ITU group compared with non-COVID-19 ITU disease control patients and that autoantibodies were also found in the serum 3–5 months post-COVID-19 infection. Non-COVID patients displayed a diverse pattern of autoantibodies; in contrast, the COVID-19 groups had a more restricted panel of autoantibodies including skin, skeletal muscle and cardiac antibodies. Our results demonstrate that respiratory viral infection with SARS-CoV-2 is associated with the detection of a limited profile of tissue-specific autoantibodies, detectable using routine clinical immunology assays. Further studies are required to determine whether these autoantibodies are specific to SARS-CoV-2 or a phenomenon arising from severe viral infections and to determine the clinical significance of these autoantibodies.

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Rejuvenation Res. 2021 Jul 1. doi: 10.1089/rej.2021.0038. Online ahead of print.

The Dilution Conundrum of Longevity

Victor Björk [1]

Affiliations + expand

PMID: 34210165 DOI: 10.1089/rej.2021.0038

Abstract

The emerging longevity industry faces challenges to it's resource management, here four major risks are discussed.

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New study finds most adults would not take a life extension pill, even if it existed

By Douglas Heingartner ○ June 6, 2021

A new study of about 900 U.S. adults has found that only 33% would use a hypothetical life extension treatment that would allow them "to live forever," even if it were available today. About 42% said they would not use it, and 25% said they were unsure.

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PEARL Is Funded, Rapamycin Longevity Clinical Trials Begin

We have achieved every stretch goal of the PEARL crowdfunding project!

By **Steve Hill** *June 18, 2021*

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PEARL: PARTICIPATORY EVALUATION OF AGING WITH RAPAMYCIN FOR LONGEVITY

The first large-scale placebo-controlled clinical trial to determine the effects of Rapamycin on human longevity.

BY DR. SAJAD ZALZALA

Funding Successful. This project reached its goal before June 17, 2021.

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New journal: The Lancet Healthy Longevity

Editorial > Lancet Healthy Longev. 2020 Oct;1(1):e1. doi: 10.1016/S2666-7568(20)30022-2. Epub 2020 Oct 20.

The Lancet Healthy Longevity: Health For All, For Longer

The Lancet Healthy Longevity

PMID: 34173608 PMCID: PMC7574773 DOI: 10.1016/S2666-7568(20)30022-2

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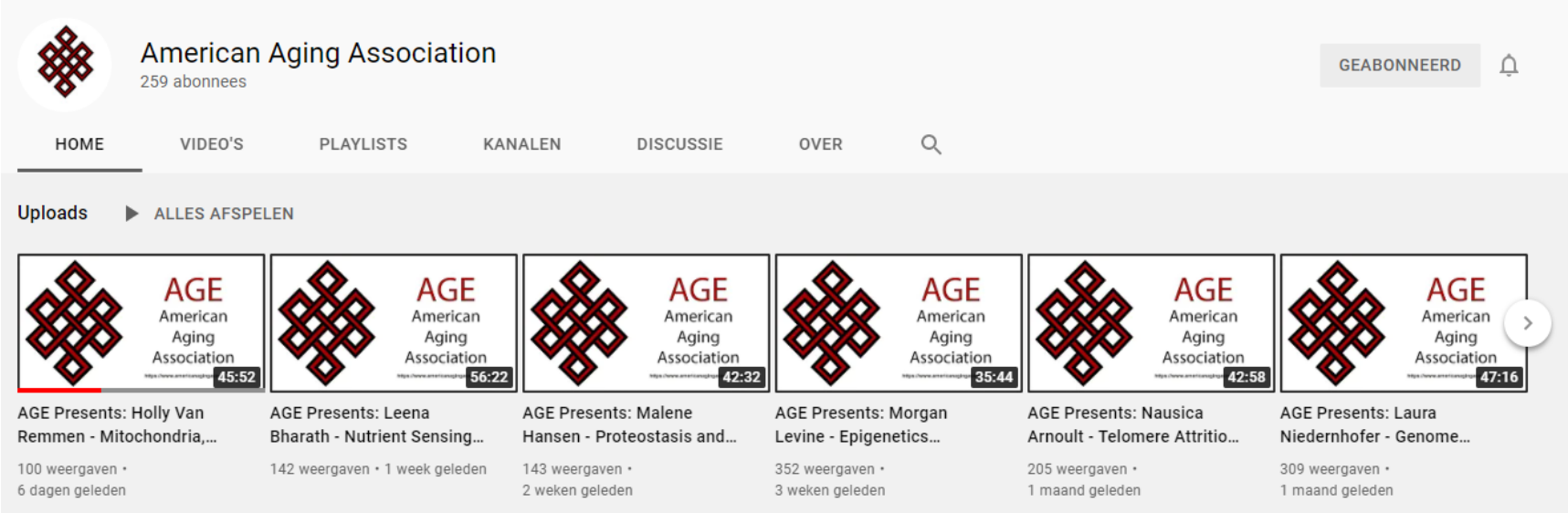

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Biogen's aducanumab crosses FDA finish line just in time to save its business

by Noah Higgins-Dunn | Jun 7, 2021 11:03am

The FDA approved Biogen's controversial Alzheimer's hopeful aducanumab at a time when the company faces serious troubles elsewhere in its business. (Biogen)

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ARDD 2021

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31 AUGUST — 3 SEPTEMBER

30 AUGUST — LONGEVITY MEDICINE WORKSHOP

According to the United Nations, the proportion of people aged over 65 now outnumber children younger than 5. The enormous growth in the elderly population is posing a socioeconomic challenge to societies worldwide, and necessitates new sweeping interventions for age-associated diseases. This year we have an incredibly exciting program with global thought-leaders sharing their latest insights into aging and how we target aging process ensuring everyone lives a healthier and longer life. Welcome to the 8th Aging Research and Drug Discovery Meeting.

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CONFERENCE. BIG DATA, A.I. AND HEALTHY LONGEVITY. HOW TO PROGRESS FASTER AND BETTER FOR ALL SCIENTISTS? THURSDAY SEPTEMBER 9, 2021

MAI 28, 2021 DIDIERCOEURNELLE

Joint Heales and International Longevity Alliance (online) conference on Thursday, September 9 from 5-10pm CET (Brussels), 8 am-1pm PDT (San Francisco), titled:

Big Data, A.I. and Healthy Longevity.

Aging research articles

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The long lives of primates and the 'invariant rate of ageing' hypothesis

Fernando Colchero, José Manuel Aburto, [...]Susan C. Alberts

Nature Communications **12**, Article number: 3666 (2021) | Cite this article

Abstract

Is it possible to slow the rate of ageing, or do biological constraints limit its plasticity? We test the 'invariant rate of ageing' hypothesis, which posits that the rate of ageing is relatively fixed within species, with a collection of 39 human and nonhuman primate datasets across seven genera. We first recapitulate, in nonhuman primates, the highly regular relationship between life expectancy and lifespan equality seen in humans. We next demonstrate that variation in the rate of ageing within genera is orders of magnitude smaller than variation in pre-adult and age-independent mortality. Finally, we demonstrate that changes in the rate of ageing, but not other mortality parameters, produce striking, species-atypical changes in mortality patterns. Our results support the invariant rate of ageing hypothesis, implying biological constraints on how much the human rate of ageing can be slowed.

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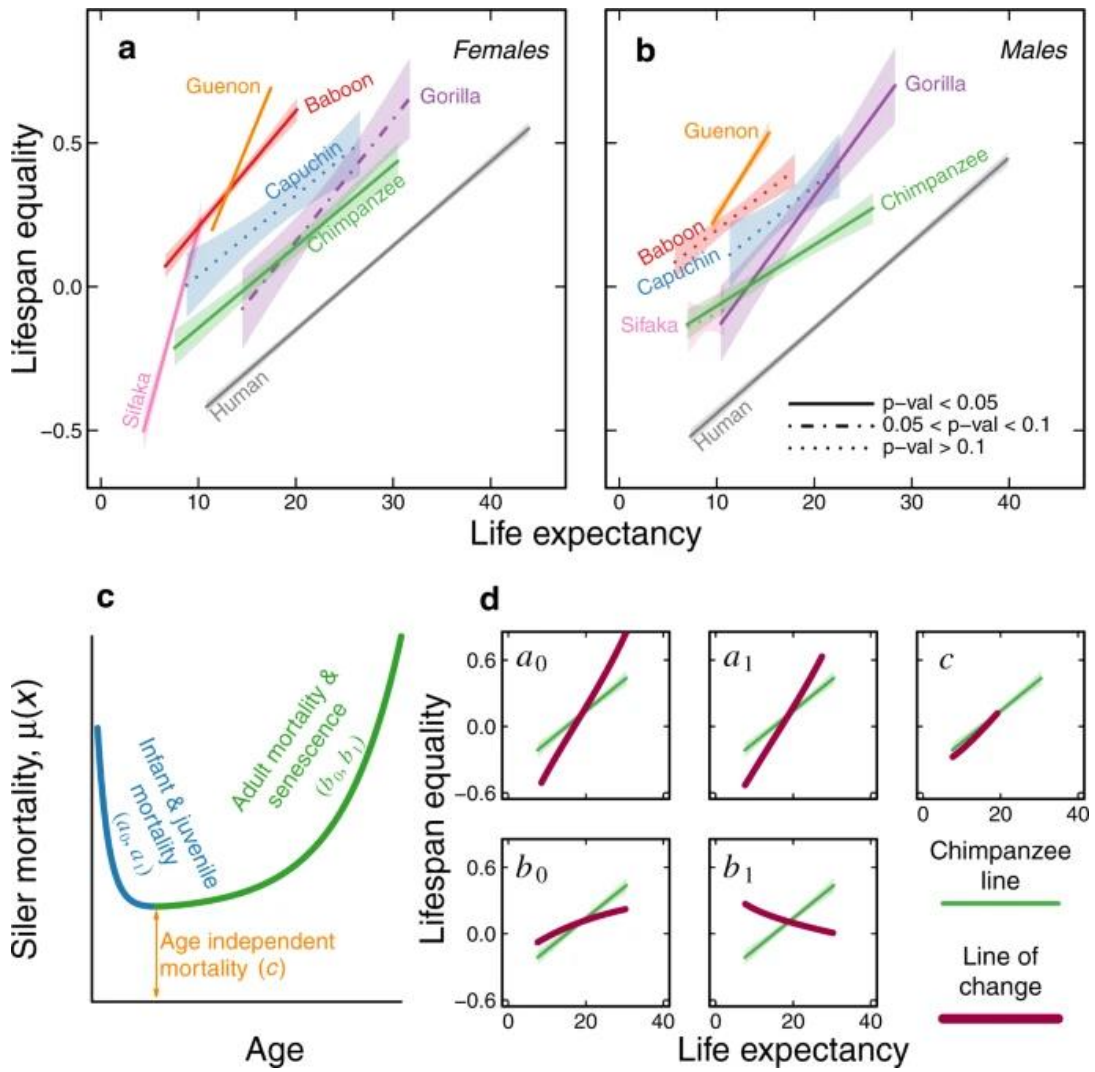
$$\mu(x) = \exp(a_0 - a_1 x) + c + \exp(b_0 + b_1 x), \quad for\ x \geq 0$$



Colchero et al.[13]. These nine populations had not benefited from modern advances in public health, medicine, and standards of living, enabling us to carry out the most salient comparisons with nonhuman primates. We use life tables from the Human Mortality Database[19] for **(1)** Sweden from 1751 to 1759, **(2)** Sweden in 1773, **(3)** Sweden from 1850 to 1859, **(4)** and Iceland in 1882. We also use human life tables for **(5)** England from 1600 to 1725[20], **(6)** Trinidad from 1813 to 1815[21], **(7)** Ukraine in 1933[22] and two hunter gatherer populations, **(8)** the Hadza, based on data collected between 1985 and 2000[23] and **(9)** the Ache during the pre-contact period of 1900–1978[24]. In the aggregate, our 39 combined

Finally, can we humans slow our own rate of ageing? Our findings support the idea that, in historical population when life expectancies were low, mortality improvements for infants, and in age-independent mortality, were the central contributors to the decades-long trend towards longer human life expectancies and greater lifespan equality[3]. These improvements were largely the result of environmental influences including social, economic, and public health advances[13,34,35]. Since the middle of the 20th century, however, declines in the baseline level of adult mortality—measured in the context of the Siler model by b_0—have very likely played an increasingly important role in industrialised societies[3,8]. As we show here, improvements in the environment are unlikely to translate into a substantial reduction in the rate of ageing, b_1, or in the dramatic increase in lifespan that would result from such a change. It remains to be seen if future advances in medicine can overcome the biological constraints that we have identified here, and achieve what evolution has not.

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PREPRINT

New intranasal and injectable gene therapy for healthy life extension

Dabbu Kumar Jaijyan, Anca Selariu, Ruth Cruz-Cosme, Mingming Tong, Shaomin Yang, George Church, David Kekich, Ali Fallah, Junichi Sadoshima, Qiyi Tang, Elizabeth Parrish, Hua Zhu

doi: https://doi.org/10.1101/2021.06.26.449305

Abstract

As the global elderly population grows, it is socioeconomically and medically critical to have diverse and effective means of mitigating the impact of aging on human health. Previous studies showed that adenovirus-associated virus (AAV) vector induced overexpression of certain proteins can suppress or reverse the effects of aging in animal models. Here, we sought to determine whether the high-capacity cytomegalovirus vector can be an effective and safe gene delivery method for two such-protective factors: telomerase reverse transcriptase (TERT) and follistatin (FST). We found that the mouse cytomegalovirus (MCMV) carrying exogenous TERT or FST ($MCMV_{TERT}$ or $MCMV_{FST}$) extended median lifespan by 41.4% and 32.5%, respectively. This is the first report of CMV being used successfully as both an intranasal and injectable gene therapy system to extend longevity. Treatment significantly improved glucose tolerance, physical performance, and prevented loss of body mass and alopecia. Telomere shortening seen with aging was ameliorated by TERT, and mitochondrial structure deterioration was halted in both treatments. Intranasal and injectable preparations performed equally well in safely and efficiently delivering gene therapy to multiple organs, with long-lasting benefits and without carcinogenicity or unwanted side effects. Translating this research to humans could have significant benefits associated with increased health span.

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Senolytics reduce coronavirus-related mortality in old mice

Christina D. Camell[1,†], Matthew J. Yousefzadeh[1,†], Yi Zhu[2,3,†], Larissa G. P. Langhi Prata[2,†], Matthew A. Hug...
+ See all authors and affiliations

Science 08 Jun 2021:
eabe4832
DOI: 10.1126/science.abe4832

Abstract

The COVID-19 pandemic has revealed the pronounced vulnerability of the elderly and chronically-ill to SARS-CoV-2-induced morbidity and mortality. Cellular senescence contributes to inflammation, multiple chronic diseases, and age-related dysfunction, but effects on responses to viral infection are unclear. Here, we demonstrate that senescent cells (SnC) become hyper-inflammatory in response to pathogen-associated molecular patterns (PAMPs), including SARS-CoV-2 Spike protein-1, increasing expression of viral entry proteins and reducing anti-viral gene expression in non-SnCs through a paracrine mechanism. Old mice acutely infected with pathogens that included a SARS-CoV-2-related mouse β-coronavirus experienced increased senescence and inflammation with nearly 100% mortality. Targeting SnCs using senolytic drugs before or after pathogen exposure significantly reduced mortality, cellular senescence, and inflammatory markers and increased anti-viral antibodies. Thus, reducing the SnC burden in diseased or aged individuals should enhance resilience and reduce mortality following viral infection, including SARS-CoV-2.

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Senolytics alleviate the degenerative disorders of temporomandibular joint in old age

Yueying Zhou, Iman M. A. Al-Naggar, Po-Jung Chen, Nathan S. Gasek, Ke Wang, Shivam Mehta, George A. Kuchel, Sumit Yadav ✉, Ming Xu ✉

Aging is one of the major risk factors for degenerative joint disorders, including those involving the temporomandibular joint (TMJ). TMJ degeneration occurs primarily in the population over 65, significantly increasing the risk of joint discomfort, restricted joint mobility, and reduced quality of life. Unfortunately, there is currently no effective mechanism-based treatment available in the clinic to alleviate TMJ degeneration with aging. We now demonstrate that intermittent administration of senolytics, drugs which can selectively clear senescent cells, preserved mandibular condylar cartilage thickness, improved subchondral bone volume and turnover, and reduced Osteoarthritis Research Society International (OARSI) histopathological score in both 23- to 24-month-old male and female mice. Senolytics had little effect on 4 months old young mice, indicating age-specific benefits. Our study provides proof-of-concept evidence that age-related TMJ degeneration can be alleviated by pharmaceutical intervention targeting cellular senescence. Since the senolytics used in this study have been proven relatively safe in recent human studies, our findings may help justify future clinical trials addressing TMJ degeneration in old age.

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Senolytics improve bone forming potential of bone marrow mesenchymal stem cells from aged mice

Yueying Zhou[1,2,3], Xiaonan Xin[3], Lichao Wang[2,4], Binsheng Wang[2,4], Li Chen[3], Ousheng Liu[1], David W. Rowe[3]✉ and Ming Xu[2,4]✉

The osteogenic potential of bone marrow mesenchymal stem cells (BMSCs) declines dramatically with aging. By using a calvarial defect model, we showed that a senolytic cocktail (dasatinib+quercetin; D + Q) improved osteogenic capacity of aged BMSC both in vitro and in vivo. The study presented a model to assess strategies to improve bone-forming potential on aged BMSCs. D + Q might hold promise for improving BMSC function in aged populations.

npj Regenerative Medicine (2021)6:34; https://doi.org/10.1038/s41536-021-00145-z

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The American lobster genome reveals insights on longevity, neural, and immune adaptations

Abstract

The American lobster, *Homarus americanus*, is integral to marine ecosystems and supports an important commercial fishery. This iconic species also serves as a valuable model for deciphering neural networks controlling rhythmic motor patterns and olfaction. Here, we report a high-quality draft assembly of the *H. americanus* genome with 25,284 predicted gene models. Analysis of the neural gene complement revealed extraordinary development of the chemosensory machinery, including a profound diversification of ligand-gated ion channels and secretory molecules. The discovery of a novel class of chimeric receptors coupling pattern recognition and neurotransmitter binding suggests a deep integration between the neural and immune systems. A robust repertoire of genes involved in innate immunity, genome stability, cell survival, chemical defense, and cuticle formation represents a diversity of defense mechanisms essential to thrive in the benthic marine environment. Together, these unique evolutionary adaptations contribute to the longevity and ecological success of this long-lived benthic predator.

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Epigenetic clock and methylation studies in elephants

Natalia A. Prado, Janine L. Brown, Joseph A. Zoller, Amin Haghani, Mingjia Yao, Lora R. Bagryanova, Michael G. Campana, Jesús E. Maldonado ✉, Ken Raj, Dennis Schmitt, Todd R. Robeck, Steve Horvath ✉

Age-associated DNA-methylation profiles have been used successfully to develop highly accurate biomarkers of age ("epigenetic clocks") in humans, mice, dogs, and other species. Here we present epigenetic clocks for African and Asian elephants. These clocks were developed using novel DNA methylation profiles of 140 elephant blood samples of known age, at loci that are highly conserved between mammalian species, using a custom Infinium array (HorvathMammalMethylChip40). We present epigenetic clocks for Asian elephants (*Elephas maximus*), African elephants (*Loxodonta africana*), and both elephant species combined. Two additional human-elephant clocks were constructed by combining human and elephant samples. Epigenome-wide association studies identified elephant age-related CpGs and their proximal genes. The products of these genes play important roles in cellular differentiation, organismal development, metabolism, and circadian rhythms. Intracellular events observed to change with age included the methylation of bivalent chromatin domains, and targets of polycomb repressive complexes. These readily available epigenetic clocks can be used for elephant conservation efforts where accurate estimates of age are needed to predict demographic trends.

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Homocysteine fibrillar assemblies display cross-talk with Alzheimer's disease β-amyloid polypeptide

High levels of homocysteine are reported as a risk factor for Alzheimer's disease (AD). Correspondingly, inborn hyperhomocysteinemia is associated with an increased predisposition to the development of dementia in later stages of life. Yet, the mechanistic link between homocysteine accumulation and the pathological neurodegenerative processes is still elusive. Furthermore, despite the clear association between protein aggregation and AD, attempts to develop therapy that specifically targets this process have not been successful. It is envisioned that the failure in the development of efficacious therapeutic intervention may lie in the metabolomic state of affected individuals. We recently demonstrated the ability of metabolites to self-assemble and cross-seed the aggregation of pathological proteins, suggesting a role for metabolite structures in the initiation of neurodegenerative diseases. Here, we provide a report of homocysteine crystal structure and self-assembly into amyloid-like toxic fibrils, their inhibition by polyphenols, and their ability to seed the aggregation of the AD-associated β-amyloid polypeptide. A yeast model of hyperhomocysteinemia indicates a toxic effect, correlated with increased intracellular amyloid staining that could be rescued by polyphenol treatment. Analysis of AD mouse model brain sections indicates the presence of homocysteine assemblies and the interplay between β-amyloid and homocysteine. This work implies a molecular basis for the association between homocysteine accumulation and AD pathology, potentially leading to a paradigm shift in the understanding of AD initial pathological processes.

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Biogenic metallic elements in the human brain?

James Everett[1,2], Frederik Lermyte[2,3], Jake Brooks[2], Vindy Tjendana-Tjhin[2], Germán Plascencia-Villa[4], Ian ...
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Article | Figures & Data | Info & Metrics | eLetters | PDF

Abstract

The chemistry of copper and iron plays a critical role in normal brain function. A variety of enzymes and proteins containing positively charged Cu^{+}, Cu^{2+}, Fe^{2+}, and Fe^{3+} control key processes, catalyzing oxidative metabolism and neurotransmitter and neuropeptide production. Here, we report the discovery of elemental (zero–oxidation state) metallic Cu^{0} accompanying ferromagnetic elemental Fe^{0} in the human brain. These nanoscale biometal deposits were identified within amyloid plaque cores isolated from Alzheimer's disease subjects, using synchrotron x-ray spectromicroscopy. The surfaces of nanodeposits of metallic copper and iron are highly reactive, with distinctly different chemical and magnetic properties from their predominant oxide counterparts. The discovery of metals in their elemental form in the brain raises new questions regarding their generation and their role in neurochemistry, neurobiology, and the etiology of neurodegenerative disease.

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Human muscle stem cells are refractory to aging

James S. Novak, Davi A. G. Mázala, Marie Nearing, Ravi Hindupur, Prech Uapinyoying, Nayab F. Habib, Tessa Dickson, Olga B. Ioffe, Brent T. Harris, Marie N. Fidelia-Lambert ... See all authors

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James S. Novak and Davi A.G. Mázala: Co-authorship: authors should be regarded as joint first authors.

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Abstract

Age-related loss of muscle mass and strength is widely attributed to limitation in the capacity of muscle resident satellite cells to perform their myogenic function. This idea contains two notions that have not been comprehensively evaluated by experiment. First, it entails the idea that we damage and lose substantial amounts of muscle in the course of our normal daily activities. Second, it suggests that mechanisms of muscle repair are in some way exhausted, thus limiting muscle regeneration. A third potential option is that the aged environment becomes inimical to the conduct of muscle regeneration. In the present study, we used our established model of human muscle xenografting to test whether muscle samples taken from cadavers, of a range of ages, maintained their myogenic potential after being transplanted into immunodeficient mice. We find no measurable difference in regeneration across the range of ages investigated up to 78 years of age. Moreover, we report that satellite cells maintained their myogenic capacity even when muscles were grafted 11 days postmortem in our model. We conclude that the loss of muscle mass with increasing age is not attributable to any intrinsic loss of myogenicity and is most likely a reflection of progressive and detrimental changes in the muscle microenvironment such as to disfavor the myogenic function of these cells.

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Synergistic sequence contributions bias glycation outcomes

Joseph M. McEwen, Sasha Fraser, Alexxandra L. Sosa Guir, Jaydev Dave & Rebecca A. Scheck

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Abstract

The methylglyoxal-derived hydroimidazolone isomer, MGH-1, is an abundant advanced glycation end-product (AGE) associated with disease and age-related disorders. As AGE formation occurs spontaneously and without an enzyme, it remains unknown why certain sites on distinct proteins become modified with specific AGEs. Here, we use a combinatorial peptide library to determine the chemical features that favor MGH-1. When properly positioned, tyrosine is found to play an active mechanistic role that facilitates MGH-1 formation. This work offers mechanistic insight connecting multiple AGEs, including MGH-1 and carboxyethylarginine (CEA), and reconciles the role of negative charge in influencing glycation outcomes. Further, this study provides clear evidence that glycation outcomes can be influenced through long- or medium-range cooperative interactions. This work demonstrates that these chemical features also predictably template selective glycation on full-length protein targets expressed in mammalian cells. This information is vital for developing methods that control glycation in living cells and will enable the study of glycation as a functional post-translational modification.

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No association between frailty index and epigenetic clocks in Italian semi-supercentenarians

Centenarians experience successful ageing, although they still present high heterogeneity in their health status. The frailty index is a biomarker of biological age, able to capture such heterogeneity, even at extreme old age. At the same time, other biomarkers (e.g., epigenetic clocks) may be informative the biological age of the individual and potentially describe the ageing status in centenarians. In this article, we explore the relationship between epigenetic clocks and frailty index in a cohort of Italian centenarians. No association was reported, suggesting that these two approaches may describe different aspects of the same ageing process.

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Genetic Analyses of Epigenetic Predictors that Estimate Aging, Metabolic Traits, and Lifespan

Khyobeni Mozhui, Ake T. Lu, Caesar Z Li, Amin Haghani, Jose Vladimir Sandoval-Sierra, Robert W. Williams, Steve Horvath

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Abstract

DNA methylation (DNAm) clocks are accurate molecular biomarkers of aging. However, the clock mechanisms remain unclear. Here, we used a pan-mammalian microarray to assay DNAm in liver from 339 predominantly female mice belonging to the BXD family. We computed epigenetic clocks and maximum lifespan predictor (predicted-maxLS), and examined associations with DNAm entropy, diet, weight, metabolic traits, and genetic variation. The epigenetic age acceleration (EAA) derived from the clocks, and predicted-maxLS were correlated with lifespan of the BXD strains. Quantitative trait locus (QTL) analyses uncovered significant QTLs on chromosome (Chr) 11 that encompasses the *Erbb2/Her2* oncogenic region, and on Chr19 that contains a cytochrome P450 cluster. Both loci harbor candidate genes associated with EAA in humans (*STXBP4*, *NKX2*-3, *CUTC*). Transcriptome and proteome analyses revealed enrichment in oxidation-reduction, metabolic, and mitotic genes. Our results highlight loci that are concordant in human and mouse, and demonstrate intimate links between metabolism, body weight, and epigenetic aging.

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

Daniel L. McCartney, Josine L. Min, [...]Riccardo E. Marioni

Background

Biological aging estimators derived from DNA methylation data are heritable and correlate with morbidity and mortality. Consequently, identification of genetic and environmental contributors to the variation in these measures in populations has become a major goal in the field.

Results

Leveraging DNA methylation and SNP data from more than 40,000 individuals, we identify 137 genome-wide significant loci, of which 113 are novel, from genome-wide association study (GWAS) meta-analyses of four epigenetic clocks and epigenetic surrogate markers for granulocyte proportions and plasminogen activator inhibitor 1 levels, respectively. We find evidence for shared genetic loci associated with the Horvath clock and expression of transcripts encoding genes linked to lipid metabolism and immune function. Notably, these loci are independent of those reported to regulate DNA methylation levels at constituent clock CpGs. A polygenic score for GrimAge acceleration showed strong associations with adiposity-related traits, educational attainment, parental longevity, and C-reactive protein levels.

Conclusion

This study illuminates the genetic architecture underlying epigenetic aging and its shared genetic contributions with lifestyle factors and longevity.

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PREPRINT

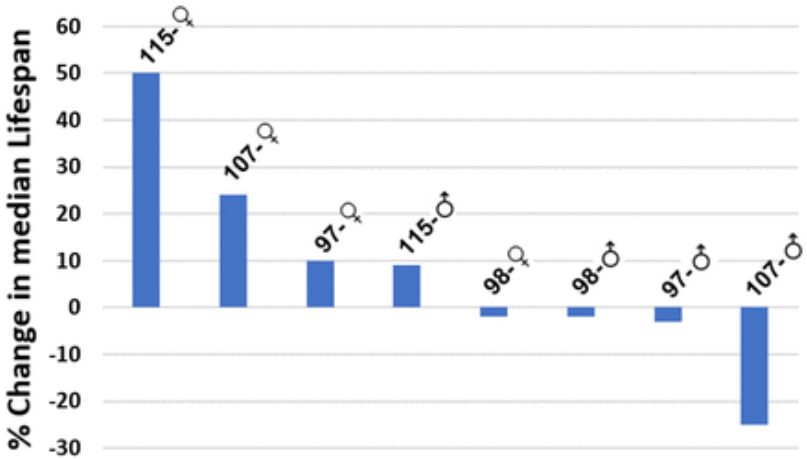
A Reevaluation of the Effect of Dietary Restriction on Different Recombinant Inbred (RI) Lines of Male and Female Mice

Archana Unnikrishnan, Stephanie Matyi, Karla Garrett, Michelle Ranjo-Bishop, David B Allison, Keisuke Ejima, Xiwei Chen, Stephanie Dickinson, Arlan Richardson

doi: https://doi.org/10.1101/2021.06.25.449984

Abstract

Dietary restriction (DR) was reported to either have no effect or reduced the lifespan of the majority of the 41-recombinant inbred (RI)-lines studied (Liao et al., 2010). In an appropriately power longevity study (n > 30 mice/group), we measured the lifespan of the four RI-lines (115-RI, 97-RI, 98-RI, and 107-RI) that were reported to have the greatest decrease in lifespan when fed 40% DR. DR increased the median lifespan of female and male 115-RI mice and female 97-RI and 107-RI mice. DR had little effect (less than 4%) on the median lifespan of female and male 98-RI mice and male 97-RI mice and reduced the lifespan of male 107-RI mice over 20%. While our study was unable to replicate the effect of DR on the lifespan of the RI-mice (except male 107-RI mice) reported by Liao et al. (2010), we found that the genotype of a mouse had a major impact on the effect of DR on lifespan, with the effect of DR ranging from a 50% increase to a 22% decrease. No correlation was observed between the changes in either body composition or glucose tolerance induced by DR and the changes observed in lifespan of the four RI-lines of male and female mice. These four RI-lines of mice give the research community a unique resource where investigators for the first time can study the anti-aging mechanism of DR by comparing mice in which DR increases lifespan to mice where DR has either no effect or reduces lifespan.



C. elegans aging research

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PREPRINT

Prediction of biological age by morphological staging of sarcopenia in *Caenorhabditis elegans*

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Abstract

Sarcopenia encompasses a progressive decline in allover muscle quantity and quality. Given its close association with aging, it may represent a valuable healthspan marker. Given the strong commonalities with human muscle structure and the facile visualization possibilities, *C. elegans* represents an attractive model for studying the relationship between sarcopenia and healthspan. However, classical assessment relies on visual scoring of muscle architecture, which is subjective and inaccurate. To resolve this, we have developed an automated image analysis pipeline for the detailed quantification and classification of muscle integrity in confocal microscopy images from a cohort of aging myosin::GFP reporter strains. We then extracted a variety of morphological descriptors and found a subset to scale linearly with age. This allowed us to establish a general linear model that predicts biological age from a morphological muscle signature. To validate the model, we evaluated muscle architecture in long-lived worms that are known to experience delayed sarcopenia by targeted RNAi-mediated knockdown of the *daf-2* gene. We conclude that quantitative microscopy allows for staging sarcopenia in *C. elegans* and will be of use for systematic screening for pharmacological or genetic modulators that mitigate age-related muscle frailty and thus improve healthspan in *C. elegans*.

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Small flexible automated system for monitoring *Caenorhabditis elegans* lifespan based on active vision and image processing techniques

Joan Carles Puchalt, Antonio-José Sánchez-Salmerón, Eugenio Ivorra, Silvia Llopis, Roberto Martínez & Patricia Martorell

Traditionally *Caenorhabditis elegans* lifespan assays are performed by manually inspecting nematodes with a dissection microscope, which involves daily counting of live/dead worms cultured in Petri plates for 21–25 days. This manual inspection requires the screening of hundreds of worms to ensure statistical robustness, and is therefore a time-consuming approach. In recent years, various automated artificial vision systems have been reported to increase the throughput, however they usually provide less accurate results than manual assays. The main problems identified when using these vision systems are the false positives and false negatives, which occur due to culture media changes, occluded zones, dirtiness or condensation of the Petri plates. In this work, we developed and described a new *C. elegans* monitoring machine, SiViS, which consists of a flexible and compact platform design to analyse *C. elegans* cultures using the standard Petri plates seeded with *E. coli*. Our system uses an active vision illumination technique and different image-processing pipelines for motion detection, both previously reported, providing a fully automated image processing pipeline. In addition, this study validated both these methods and the feasibility of the SiViS machine for lifespan experiments by comparing them with manual lifespan assays. Results demonstrated that the automated system yields consistent replicates (p-value log rank test 0.699), and there are no significant differences between automated system assays and traditionally manual assays (p-value 0.637). Finally, although we have focused on the use of SiViS in longevity assays, the system configuration is flexible and can, thus, be adapted to other *C. elegans* studies such as toxicity, mobility and behaviour.

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Two human metabolites rescue a C. elegans model of Alzheimer's disease via a cytosolic unfolded protein response

Abstract

Age-related changes in cellular metabolism can affect brain homeostasis, creating conditions that are permissive to the onset and progression of neurodegenerative disorders such as Alzheimer's and Parkinson's diseases. Although the roles of metabolites have been extensively studied with regard to cellular signaling pathways, their effects on protein aggregation remain relatively unexplored. By computationally analysing the Human Metabolome Database, we identified two endogenous metabolites, carnosine and kynurenic acid, that inhibit the aggregation of the amyloid beta peptide (Aβ) and rescue a C. elegans model of Alzheimer's disease. We found that these metabolites act by triggering a cytosolic unfolded protein response through the transcription factor HSF-1 and downstream chaperones HSP40/J-proteins DNJ-12 and DNJ-19. These results help rationalise previous observations regarding the anti-ageing benefits of these metabolites, by providing a mechanism for their action. Our findings provide a link between metabolite homeostasis and protein homeostasis, which could inspire preventative interventions against neurodegenerative disorders.

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Neuronal DAF-16-to-intestinal DAF-16 communication underlies organismal lifespan extension in *C. elegans*

Previous studies have revealed the importance of inter-tissue communications for lifespan regulation. However, the inter-tissue network responsible for lifespan regulation is not well understood, even in a simple organism *Caenorhabditis elegans*. To understand the mechanisms underlying systemic lifespan regulation, we focused on lifespan regulation by the insulin/insulin-like growth factor-1 signaling (IIS) pathway; IIS reduction activates the DAF-16/FOXO transcription factor, which results in lifespan extension. Our tissue-specific knockdown and knockout analyses demonstrated that IIS reduction in neurons and the intestine markedly extended lifespan. DAF-16 activation in neurons resulted in DAF-16 activation in the intestine and vice versa. Our dual gene manipulation method revealed that intestinal and neuronal DAF-16 mediate longevity induced by *daf-2* knockout in neurons and the intestine, respectively. In addition, the systemic regulation of intestinal DAF-16 required the IIS pathway in intestinal and neurons. Collectively, these results highlight the importance of the neuronal DAF-16-to-intestinal DAF-16 communication for organismal lifespan regulation.

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Overcoming Autofluorescence to Assess GFP Expression During Normal Physiology and Aging in *Caenorhabditis elegans*

Alina C. Teuscher and Collin Y. Ewald

Green fluorescent protein (GFP) is widely used as a molecular tool to assess protein expression and localization. In *C. elegans*, the signal from weakly expressed GFP fusion proteins is masked by autofluorescence emitted from the intestinal lysosome-related gut granules. For instance, the GFP fluorescence from SKN-1 transcription factor fused to GFP is barely visible with common GFP (FITC) filter setups. Furthermore, this intestinal autofluorescence increases upon heat stress, oxidative stress (sodium azide), and during aging, thereby masking GFP expression even from proximal tissues. Here, we describe a triple band GFP filter setup that separates the GFP signal from autofluorescence, displaying GFP in green and autofluorescence in yellow. In addition, yellow fluorescent protein (YFP) remains distinguishable from both the yellowish autofluorescence and GFP with this triple band filter setup. Although some GFP intensity might be lost with the triple band GFP filter setup, the advantage is that no modification of currently used transgenic GFP lines is needed and these GFP filters are easy to install. Hence, by using this triple band GFP filter setup, the investigators can easily distinguish autofluorescence from GFP and YFP in their favorite transgenic *C. elegans* lines.

Keywords: Microscopy, Filter set, Fluorescent protein, GFP, YFP, Autofluorescence, Gut granules, Lysosome-related organelles, Age-pigments, Lipofuscin, Aging, Transcription factor, SKN-1, HSF-1, *C. elegans*

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Autofluorescence as a noninvasive biomarker of senescence and advanced glycation end products in *Caenorhabditis elegans*

Tomomi Komura[1,2], Mikihiro Yamanaka[3], Kohji Nishimura[4,5], Keita Hara[6] and Yoshikazu Nishikawa[2,7]✉

To assess the utility of autofluorescence as a noninvasive biomarker of senescence in *Caenorhabditis elegans*, we measured the autofluorescence of individual nematodes using spectrofluorometry. The fluorescence of each worm increased with age. Animals with lower fluorescence intensity exhibited longer life expectancy. When proteins extracted from worms were incubated with sugars, the fluorescence intensity and the concentration of advanced glycation end products (AGEs) increased over time. Ribose enhanced these changes not only in vitro but also in vivo. The glycation blocker rifampicin suppressed this rise in fluorescence. High-resolution mass spectrometry revealed that vitellogenins accumulated in old worms, and glycated vitellogenins emitted six-fold higher fluorescence than naive vitellogenins. The increase in fluorescence with ageing originates from glycated substances, and therefore could serve as a useful noninvasive biomarker of AGEs. *C. elegans* can serve as a new model to look for anti-AGE factors and to study the relationship between AGEs and senescence.

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REVIEWS/COMMENTS/ METHODS/EDITORIALS

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An essay on the nominal vs. real definitions of aging

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Affiliations + expand

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Free PMC article

Abstract

In the current literature, the definitions of aging range from relying on certain sets of distinctive features at the molecular, organismal, populational and/or even evolutional levels/scales to declaring it a treatable disease and, moreover, to treating aging as a mental construct rather than a natural phenomenon. One reason of such a mess may be that it is common in the natural sciences to disregard philosophy of science where several categories of definitions are recognized, among which the nominal are less, and the so-called real ones are more appropriate in scientific contexts. E.g., water is, by its nominal definition, a liquid having certain observable features and, by its real definition, a specific combination (or a product of interaction) of hydrogen and oxygen atoms. Noteworthy, the real definition is senseless for people ignorant of atoms. Likewise, the nominal definition of aging as a set of observable features should be supplemented, if not replaced, with its real definition. The latter is suggested here to imply that aging is the product of chemical interactions between the rapidly turning-over free metabolites and the slowly turning-over metabolites incorporated in macromolecules involved in metabolic control. The phenomenon defined in this way emerged concomitantly with metabolic pathways controlled by enzymes coded for by information-storing macromolecules and is inevitable wherever such conditions coincide. Aging research, thus, is concerned with the elucidation of the pathways and mechanisms that link aging defined as above to its hallmarks and manifestations, including those comprised by its nominal definitions. Esoteric as it may seem, defining aging is important for deciding whether aging is what should be declared as the target of interventions aimed at increasing human life and health spans.

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Inflammation, epigenetics, and metabolism converge to cell senescence and ageing: the regulation and intervention

Xudong Zhu, Zhiyang Chen, Weiyan Shen, Gang Huang, John M. Sedivy, Hu Wang & Zhenyu Ju

Signal Transduction and Targeted Therapy **6**, Article number: 245 (2021) | Cite this article

Abstract

Remarkable progress in ageing research has been achieved over the past decades. General perceptions and experimental evidence pinpoint that the decline of physical function often initiates by cell senescence and organ ageing. Epigenetic dynamics and immunometabolic reprogramming link to the alterations of cellular response to intrinsic and extrinsic stimuli, representing current hotspots as they not only (re-)shape the individual cell identity, but also involve in cell fate decision. This review focuses on the present findings and emerging concepts in epigenetic, inflammatory, and metabolic regulations and the consequences of the ageing process. Potential therapeutic interventions targeting cell senescence and regulatory mechanisms, using state-of-the-art techniques are also discussed.

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Senotherapeutics: Targeting senescent cells for the main age-related diseases

Virginia Boccardi, Patrizia Mecocci

The review aims to summarize and discuss the current knowledge on targeting senescent cells to reduce the risk of age-related diseases in animal models and human studies. The role of cellular senescence in aging and the major age-related diseases -including Alzheimer's disease, atherosclerosis, and type 2 diabetes- as well as the use of senotherapeutic strategies in both experimental and preclinical studies, will be described. A large number of molecules, including synthetic agents and natural compounds, have been proposed for anti-senescence activities. Research on senotherapeutics, which includes senolytic and senomorphic, has a growing interest, and their safety and reliability as anti-aging drugs have been tested in clinical trials. Initial findings suggest that the senotherapeutic approach may be translatable to humans. Due to the lack of evidence, caution must be used against senolytic agents due to their potential side-effects. In this context, natural senolytic compounds should have the advantage of low toxicity and potentially more useful in humans, although the mechanisms of action need to be defined.

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The role of cellular senescence in tissue repair and regeneration

The capacity to regenerate damaged or lost tissue varies widely along the animal kingdom and generally declines with aging of the organism. The gradual accumulation of senescent cells in tissues during aging has been causally involved in their reduced function at old age, and to be at the basis of age-related diseases. Recently, however, cellular senescence has been shown to play a positive role as a morphogenetic force modelling and promoting tissue development during embryogenesis, and to be responsible for tissue wound healing and repair. Work done on organismal models ranging from fish and amphibians, with extraordinary regenerative capacities, to mammals, with a more restricted regenerative potential, is shedding light on a novel and unexpected function of cellular senescence. In this review, we will analyze the senescence phenotype and how could it be contributing or restricting tissue regeneration.

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The Role of Rapamycin in Healthspan Extension via the Delay of Organ Aging

Yan Zhang [a, b, c], Jinjin Zhang [a, b, c] ✉, Shixuan Wang [a, b, c] ✉

Aging can not only shorten a healthy lifespan, but can also lead to multi-organ dysfunction and failure. Anti-aging is a complex and worldwide conundrum for eliminating the various pathologies of senility. The past decade has seen great progress in the understanding of the aging-associated signaling pathways and their application for developing anti-aging approaches. Currently, some drugs can improve quality of life. The activation of mammalian target of rapamycin (mTOR) signaling is one of the core and detrimental mechanisms related to aging; rapamycin can reduce the rate of aging, improve age-related diseases by inhibiting the mTOR pathway, and prolong lifespan and healthspan effectively. However, the current evidence for rapamycin in lifespan extension and organ aging is fragmented and scattered. In this review, we summarize the efficacy and safety of rapamycin in prolonging a healthy lifespan by systematically alleviating aging in multiple organ systems, i.e., the nervous, urinary, digestive, circulatory, motor, respiratory, endocrine, reproductive, integumentary and immune systems, to provide a theoretical basis for the future clinical application of rapamycin in anti-aging.

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Regeneration, Rejuvenation, and Replacement: Turning Back the Clock on Tissue Aging

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Abstract

While some animals, such as planaria and hydra, appear to be capable of seemingly endless cycles of regeneration, most animals experience a gradual decline in fitness and ultimately die. The progressive loss of cell and tissue function, leading to senescence and death, is generally referred to as aging. Adult ("tissue") stem cells maintain tissue homeostasis and facilitate repair; however, age-related changes in stem cell function over time are major contributors to loss of organ function or disease in older individuals. Therefore, considerable effort is being invested in restoring stem cell function to counter degenerative diseases and age-related tissue dysfunction. Here, we will review strategies that could be used to restore stem cell function, including the use of environmental interventions, such as diet and exercise, heterochronic approaches, and cellular reprogramming. Maintaining optimal stem cell function and tissue homeostasis into late life will likely extend the amount of time older adults are able to be independent and lead healthy lives.

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Elastic fibers: formation, function, and fate during aging and disease

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Affiliations + expand

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Abstract

Elastic fibers are extracellular components of higher vertebrates and confer elasticity and resilience to numerous tissues and organs such as large blood vessels, lungs, and skin. Their formation and maturation take place in a complex multistage process called elastogenesis. It requires interactions between very different proteins but also other molecules and leads to the deposition and crosslinking of elastin's precursor on a scaffold of fibrillin-rich microfibrils. Mature fibers are exceptionally resistant to most influences and, under healthy conditions, retain their biomechanical function over the life of the organism. However, due to their longevity, they accumulate damages during aging. These are caused by proteolytic degradation, formation of advanced glycation end products, calcification, oxidative damage, aspartic acid racemization, lipid accumulation, carbamylation, and mechanical fatigue. The resulting changes can lead to diminution or complete loss of elastic fiber function and ultimately affect morbidity and mortality. Particularly, the production of elastokines has been clearly shown to influence several life-threatening diseases. Moreover, the structure, distribution, and abundance of elastic fibers are directly or indirectly influenced by a variety of inherited pathological conditions, which mainly affect organs and tissues such as skin, lungs, or the cardiovascular system. A distinction can be made between microfibril-related inherited diseases that are the result of mutations in diverse microfibril genes and indirectly affect elastogenesis, and elastinopathies that are linked to changes in the elastin gene. This review gives an overview on the formation, structure, and function of elastic fibers and their fate over the human lifespan in health and disease.

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Healthy, Active Aging for People and Dogs

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Dogs act as companions who provide us with emotional and physical support. Their shorter lifespans compel us to learn about the challenges and gifts of caring for older individuals. Our companion dogs can be exemplars of healthy or unhealthy aging, and sentinels of environmental factors that might increase or decrease our own healthy lifespan. In recent years, the field of aging has emphasized not just lifespan, but healthspan—the period of healthy, active lifespan. This focus on healthy, active aging is reflected in the World Health Organization's current focus on healthy aging for the next decade and the 2016 Healthy Aging in Action initiative in the US. This paper explores the current research into aging in both people and companion dogs, and in particular, how the relationship between older adults and dogs impacts healthy, active aging for both parties. The human-dog relationship faces many challenges as dogs, and people, age. We discuss potential solutions to these challenges, including suggestions for ways to continue contact with dogs if dog ownership is no longer possible for an older person. Future research directions are outlined in order to encourage the building of a stronger evidence base for the role of dogs in the lives of older adults.

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Footprints in the Sand: Deep Taxonomic Comparisons in Vertebrate Genomics to Unveil the Genetic Programs of Human Longevity

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With the modern quality, quantity, and availability of genomic sequencing across species, as well as across the expanse of human populations, we can screen for shared signatures underlying longevity and lifespan. Knowledge of these mechanisms would be medically invaluable in combating aging and age-related diseases. The diversity of longevities across vertebrates is an opportunity to look for patterns of genetic variation that may signal how this life history property is regulated, and ultimately how it can be modulated. Variation in human longevity provides a unique window to look for cases of extreme lifespan within a population, as well as associations across populations for factors that influence capacity to live longer. Current large cohort studies support the use of population level analyses to identify key factors associating with human lifespan. These studies are powerful in concept, but have demonstrated limited ability to resolve signals from background variation. In parallel, the expanding catalog of sequencing and annotation from diverse species, some of which have evolved longevities well past a human lifespan, provides independent cases to look at the genomic signatures of longevity. Recent comparative genomic work has shown promise in finding shared mechanisms associating with longevity among distantly related vertebrate groups. Given the genetic constraints between vertebrates, we posit that a combination of approaches, of parallel meta-analysis of human longevity along with refined analysis of other vertebrate clades having exceptional longevity, will aid in resolving key regulators of enhanced lifespan that have proven to be elusive when analyzed in isolation.

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Salamander Insights Into Ageing and Rejuvenation

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Exhibiting extreme regenerative abilities which extend to complex organs and entire limbs, salamanders have long served as research models for understanding the basis of vertebrate regeneration. Yet these organisms display additional noteworthy traits, namely extraordinary longevity, indefinite regenerative potential and apparent lack of traditional signs of age-related decay or "negligible senescence." Here, I examine existing studies addressing these features, highlight outstanding questions, and argue that salamanders constitute valuable models for addressing the nature of organismal senescence and the interplay between regeneration and ageing.

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Functional conservation in genes and pathways linking ageing and immunity

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Affiliations + expand

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Free PMC article

Abstract

At first glance, longevity and immunity appear to be different traits that have not much in common except the fact that the immune system promotes survival upon pathogenic infection. Substantial evidence however points to a molecularly intertwined relationship between the immune system and ageing. Although this link is well-known throughout the animal kingdom, its genetic basis is complex and still poorly understood. To address this question, we here provide a compilation of all genes concomitantly known to be involved in immunity and ageing in humans and three well-studied model organisms, the nematode worm Caenorhabditis elegans, the fruit fly Drosophila melanogaster, and the house mouse Mus musculus. By analysing human orthologs among these species, we identified 7 evolutionarily conserved signalling cascades, the insulin/TOR network, three MAPK (ERK, p38, JNK), JAK/STAT, TGF-β, and Nf-κB pathways that act pleiotropically on ageing and immunity. We review current evidence for these pathways linking immunity and lifespan, and their role in the detrimental dysregulation of the immune system with age, known as immunosenescence. We argue that the phenotypic effects of these pathways are often context-dependent and vary, for example, between tissues, sexes, and types of pathogenic infection. Future research therefore needs to explore a higher temporal, spatial and environmental resolution to fully comprehend the connection between ageing and immunity.

OTHER RESEARCH & REVIEWS

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CRISPR-Cas9 In Vivo Gene Editing for Transthyretin Amyloidosis

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BACKGROUND Transthyretin amyloidosis, also called ATTR amyloidosis, is a life-threatening disease characterized by progressive accumulation of misfolded transthyretin (TTR) protein in tissues, predominantly the nerves and heart. NTLA-2001 is an in vivo gene-editing therapeutic agent that is designed to treat ATTR amyloidosis by reducing the concentration of TTR in serum. It is based on the clustered regularly interspaced short palindromic repeats and associated Cas9 endonuclease (CRISPR-Cas9) system and comprises a lipid nanoparticle encapsulating messenger RNA for Cas9 protein and a single guide RNA targeting TTR.

METHODS After conducting preclinical in vitro and in vivo studies, we evaluated the safety and pharmacodynamic effects of single escalating doses of NTLA-2001 in six patients with hereditary ATTR amyloidosis with polyneuropathy, three in each of the two initial dose groups (0.1 mg per kilogram and 0.3 mg per kilogram), within an ongoing phase 1 clinical study.

RESULTS Preclinical studies showed durable knockout of TTR after a single dose. Serial assessments of safety during the first 28 days after infusion in patients revealed few adverse events, and those that did occur were mild in grade. Dose-dependent pharmacodynamic effects were observed. At day 28, the mean reduction from baseline in serum TTR protein concentration was 52% (range, 47 to 56) in the group that received a dose of 0.1 mg per kilogram and was 87% (range, 80 to 96) in the group that received a dose of 0.3 mg per kilogram.

CONCLUSIONS In a small group of patients with hereditary ATTR amyloidosis with polyneuropathy, administration of NTLA-2001 was associated with only mild adverse events and led to decreases in serum TTR protein concentrations through targeted knockout of TTR. (Funded by Intellia Therapeutics and Regeneron Pharmaceuticals; ClinicalTrials.gov number, NCT04601051.)