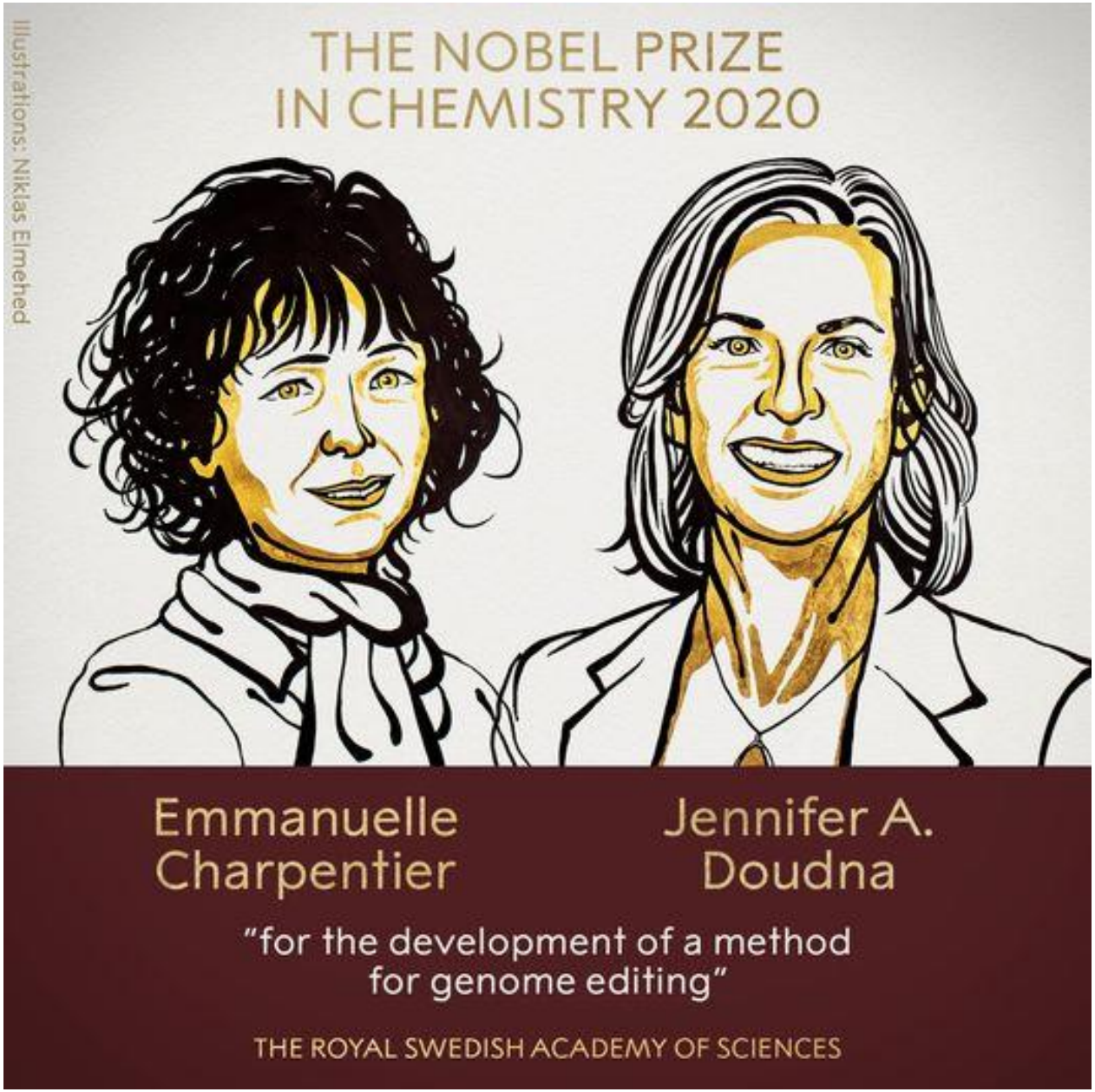
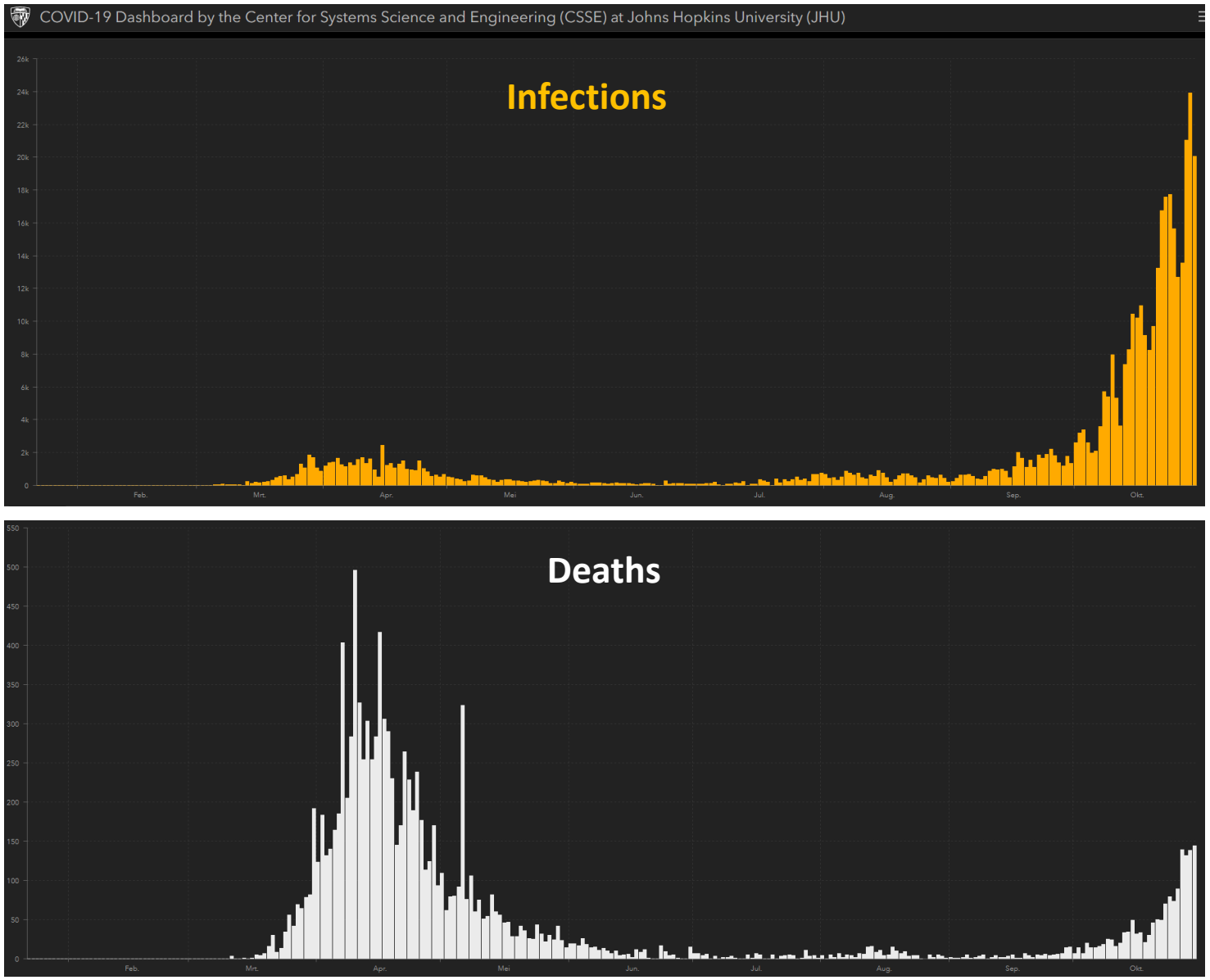
Heales
HEALTHY LIFE EXTENSION SOCIETY

Scientific News
1st of November 2020
Sven Bulterijs

Business/Conferences/ General news


THE NOBEL PRIZE
IN CHEMISTRY 2020
Illustrations: Niklas Elmehed
Emmanuelle Charpentier
Jennifer A. Doudna
"for the development of a method for genome editing"
THE ROYAL SWEDISH ACADEMY OF SCIENCES

Belgium



Regeneron's COVID-19 antibody cuts medical visits in phase 2/3 trial

Regeneron's anti-SARS-CoV-2 antibody cocktail has significantly reduced medical visits in ambulatory COVID-19 patients. The phase 2/3 clinical trial **linked** REGN-COV2 to a 57% decline in medical visits associated with COVID-19 in the 29 days after treatment.

One month ago, Regeneron shared data on the first 275 patients enrolled in the study. That update, which provided early evidence that REGN-COV2 reduces viral load, set Regeneron up to apply for FDA emergency use authorization. Now, Regeneron has shared data on an additional 525 patients to further elucidate the effect of REGN-COV2 on viral load and clinical endpoints.

The primary endpoint looked at average daily change in viral load through to Day 7 of the trial. In patients with a high viral load, REGN-COV2 drove a 0.68 log10 copies/mL greater reduction than the placebo. The effect was particularly pronounced over the first five days of the trial, over which period Regeneron linked REGN-COV2 to a tenfold reduction in viral load. A smaller, but still statistically significant, difference was seen in patients with all levels of viral load at baseline.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial)

BMJ 2020 ; 371 doi: https://doi.org/10.1136/bmj.m3939 (Published 22 October 2020)

Objective To investigate the effectiveness of using convalescent plasma to treat moderate coronavirus disease 2019 (covid-19) in adults in India.

Design Open label, parallel arm, phase II, multicentre, randomised controlled trial.

Setting 39 public and private hospitals across India.

Participants 464 adults (≥18 years) admitted to hospital (screened 22 April to 14 July 2020) with confirmed moderate covid-19 (partial pressure of oxygen in arterial blood/fraction of inspired oxygen (PaO_2/FiO_2) ratio between 200 mm Hg and 300 mm Hg or a respiratory rate of more than 24/min with oxygen saturation 93% or less on room air): 235 were assigned to convalescent plasma with best standard of care (intervention arm) and 229 to best standard of care only (control arm).

Interventions Participants in the intervention arm received two doses of 200 mL convalescent plasma, transfused 24 hours apart. The presence and levels of neutralising antibodies were not measured a priori; stored samples were assayed at the end of the study.

Main outcome measure Composite of progression to severe disease (PaO_2/FiO_2 <100 mm Hg) or all cause mortality at 28 days post-enrolment.

Results Progression to severe disease or all cause mortality at 28 days after enrolment occurred in 44 (19%) participants in the intervention arm and 41 (18%) in the control arm (risk difference 0.008 (95% confidence interval −0.062 to 0.078); risk ratio 1.04, 95% confidence interval 0.71 to 1.54).

Conclusion Convalescent plasma was not associated with a reduction in progression to severe covid-19 or all cause mortality. This trial has high generalisability and approximates convalescent plasma use in real life settings with limited laboratory capacity. A priori measurement of neutralising antibody titres in donors and participants might further clarify the role of convalescent plasma in the management of covid-19.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Efficacy of face mask in preventing respiratory virus transmission: A systematic review and meta-analysis

Background

Conflicting recommendations exist related to whether masks have a protective effect on the spread of respiratory viruses.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement was consulted to report this systematic review. Relevant articles were retrieved from PubMed, Web of Science, ScienceDirect, Cochrane Library, and Chinese National Knowledge Infrastructure (CNKI), VIP (Chinese) database.

Results

A total of 21 studies met our inclusion criteria. Meta-analyses suggest that mask use provided a significant protective effect (OR = 0.35 and 95% CI = 0.24–0.51). Use of masks by healthcare workers (HCWs) and non-healthcare workers (Non-HCWs) can reduce the risk of respiratory virus infection by 80% (OR = 0.20, 95% CI = 0.11–0.37) and 47% (OR = 0.53, 95% CI = 0.36–0.79). The protective effect of wearing masks in Asia (OR = 0.31) appeared to be higher than that of Western countries (OR = 0.45). Masks had a protective effect against influenza viruses (OR = 0.55), SARS (OR = 0.26), and SARS-CoV-2 (OR = 0.04). In the subgroups based on different study designs, protective effects of wearing mask were significant in cluster randomized trials and observational studies.

Conclusions

This study adds additional evidence of the enhanced protective value of masks, we stress that the use masks serve as an adjunctive method regarding the COVID-19 outbreak.

The effect of temperature on persistence of SARS-CoV-2 on common surfaces

Background

The rate at which COVID-19 has spread throughout the globe has been alarming. While the role of fomite transmission is not yet fully understood, precise data on the environmental stability of SARS-CoV-2 is required to determine the risks of fomite transmission from contaminated surfaces.

Methods

This study measured the survival rates of infectious SARS-CoV-2, suspended in a standard ASTM E2197 matrix, on several common surface types. All experiments were carried out in the dark, to negate any effects of UV light. Inoculated surfaces were incubated at 20 °C, 30 °C and 40 °C and sampled at various time points.

Results

Survival rates of SARS-CoV-2 were determined at different temperatures and D-values, Z-values and half-life were calculated. We obtained half lives of between 1.7 and 2.7 days at 20 °C, reducing to a few hours when temperature was elevated to 40 °C. With initial viral loads broadly equivalent to the highest titres excreted by infectious patients, viable virus was isolated for up to 28 days at 20 °C from common surfaces such as glass, stainless steel and both paper and polymer banknotes. Conversely, infectious virus survived less than 24 h at 40 °C on some surfaces.

Conclusion

These findings demonstrate SARS-CoV-2 can remain infectious for significantly longer time periods than generally considered possible. These results could be used to inform improved risk mitigation procedures to prevent the fomite spread of COVID-19.

Heales
HEALTHY LIFE EXTENSION SOCIETY

COVID-19: Effects of Environmental Conditions on the Propagation of Respiratory Droplets

As coronavirus disease 2019 (COVID-19) continues to spread, a detailed understanding on the transmission mechanisms is of paramount importance. The disease transmits mainly through respiratory droplets and aerosol. Although models for the evaporation and trajectory of respiratory droplets have been developed, how the environment impacts the transmission of COVID-19 is still unclear. In this study, we investigate the propagation of respiratory droplets and aerosol particles generated by speech under a wide range of temperatures (0–40 °C) and relative humidity (0–92%) conditions. We show that droplets can travel three times farther in low-temperature and high-humidity environment, whereas the number of aerosol particles increases in high-temperature and low-humidity environments. The results also underscore the importance of proper ventilation, as droplets and aerosol spread significantly farther in airstreams. This study contributes to the understanding of the environmental impact on COVID-19 transmission.

Heales
HEALTHY LIFE EXTENSION SOCIETY

What defines an efficacious COVID-19 vaccine? A review of the challenges assessing the clinical efficacy of vaccines against SARS-CoV-2

The novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has caused more than 1 million deaths in the first 6 months of the pandemic and huge economic and social upheaval internationally. An efficacious vaccine is essential to prevent further morbidity and mortality. Although some countries might deploy COVID-19 vaccines on the strength of safety and immunogenicity data alone, the goal of vaccine development is to gain direct evidence of vaccine efficacy in protecting humans against SARS-CoV-2 infection and COVID-19 so that manufacture of efficacious vaccines can be selectively upscaled. A candidate vaccine against SARS-CoV-2 might act against infection, disease, or transmission, and a vaccine capable of reducing any of these elements could contribute to disease control. However, the most important efficacy endpoint, protection against severe disease and death, is difficult to assess in phase 3 clinical trials. In this Review, we explore the challenges in assessing the efficacy of candidate SARS-CoV-2 vaccines, discuss the caveats needed to interpret reported efficacy endpoints, and provide insight into answering the seemingly simple question, “Does this COVID-19 vaccine work?”

Black Americans more skeptical than ever about COVID-19 vaccine: Harris Poll

by Beth Snyder Bulik | Oct 20, 2020 12:03pm

Black Americans' confidence in COVID-19 vaccines is plummeting. Only 43% of Black Americans now say they will get a vaccine once it's available, down 22 percentage points since August, The Harris Poll found.

White Americans' willingness to vaccinate has also faltered, just not as much. Currently, 58% of white people surveyed will get a vaccine when it comes out, down 11 percentage points since August.

Cellular senescence as a potential mediator of COVID−19 severity in the elderly

SARS-CoV-2 is a novel betacoronavirus which infects the lower respiratory tract and can cause coronavirus disease 2019 (COVID-19), a complex respiratory distress syndrome. Epidemiological data show that COVID-19 has a rising mortality particularly in individuals with advanced age. Identifying a functional association between SARS-CoV-2 infection and the process of biological aging may provide a tractable avenue for therapy to prevent acute and long-term disease. Here, we discuss how cellular senescence-a state of stable growth arrest characterized by pro-inflammatory and pro-disease functions-can hypothetically be a contributor to COVID-19 pathogenesis, and a potential pharmaceutical target to alleviate disease severity. First, we define why older COVID-19 patients are more likely to accumulate high levels of cellular senescence. Second, we describe how senescent cells can contribute to an uncontrolled SARS-CoV-2-mediated cytokine storm and an excessive inflammatory reaction during the early phase of the disease. Third, we discuss the various mechanisms by which senescent cells promote tissue damage leading to lung failure and multi-tissue dysfunctions. Fourth, we argue that a high senescence burst might negatively impact on vaccine efficacy. Measuring the burst of cellular senescence could hypothetically serve as a predictor of COVID-19 severity, and targeting senescence-associated mechanisms prior and after SARS-CoV-2 infection might have the potential to limit a number of severe damages and to improve the efficacy of vaccinations.

COVID-19 is an emergent disease of aging

COVID-19 is an ongoing pandemic caused by the SARS-CoV-2 coronavirus that poses one of the greatest challenges to public health in recent years. SARS-CoV-2 is known to preferentially target older subjects and those with pre-existing conditions, but the reason for this age dependence is unclear. Here, we found that the case fatality rate for COVID-19 grows exponentially with age in all countries tested, with the doubling time approaching that of all-cause human mortality. In addition, men and those with multiple age-related diseases are characterized by increased mortality. Moreover, similar mortality patterns were found for all-cause pneumonia. We further report that the gene expression of ACE2, the SARS-CoV-2 receptor, grows in the lung with age, except for subjects on a ventilator. Together, our findings establish COVID-19 as an emergent disease of aging, and age and age-related diseases as its major risk factors. In turn, this suggests that COVID-19, and deadly respiratory diseases in general, may be targeted, in addition to antiviral approaches, by approaches that target the aging process.

Heales
HEALTHY LIFE EXTENSION SOCIETY

NEWS FEATURE · 14 OCTOBER 2020

How anti-ageing drugs could boost COVID vaccines in older people

COVID-19 poses the greatest threat to older people, but vaccines often don't work well in this group. Scientists hope drugs that rejuvenate the immune system will help.

Cassandra Willyard

Older adults, like these nursing-home residents in Spain, are more vulnerable to infection and can respond poorly to vaccines. Credit: David Ramos/Getty

PDF version

RELATED ARTICLES

The race for coronavirus vaccines: a graphical guid

Who gets a COVID vaccine first? Access plans are taki shape

Genetic secrets of the heal elderly revealed

SUBJECTS

Heales
HEALTHY LIFE EXTENSION SOCIETY

Achieving healthy human longevity: A global grand challenge

Victor J. Dzau, Elizabeth M. Finkelman, Celynne A. Balatbat, Eric M. Verdin and Roderic I. Pettigrew
+ See all authors and affiliations

Science Translational Medicine 21 Oct 2020:
Vol. 12, Issue 566, eabd3816
DOI: 10.1126/scitranslmed.abd3816

Article | Figures & Data | Info & Metrics | eLetters

Abstract

With continued advances in science and technology, there is great potential to extend our healthspan as we age.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Insilico partners with Taisho on end-to-end AI-powered senolytic drug discovery

Insilico partners with Taisho Pharmaceutical on end-to-end AI-powered senolytic drug discovery. Leading Japanese pharmaceutical company to engage Insilico Medicine on research partnership in the discovery of novel molecules

INSILICO MEDICINE

Science Business Announcement

SHARE PRINT E-MAIL

Thursday, October 15, 2020 (9 am ET) - Insilico Medicine announced today that Taisho Pharmaceutical Co., Ltd. and Insilico have entered into a research collaboration to identify novel therapeutics against aging. Insilico Medicine will utilize both the target discovery and generative chemistry parts of its Pharma.AI platform in this collaboration. It will use its proprietary Pandomics Discovery Platform to identify novel targets for senolytic drugs and Chemistry42 platform for a molecular generation. This collaboration brings together Insilico's state-of-art artificial intelligence (AI) technologies in drug discovery with Taisho's expertise in drug development, aimed to extend the human healthspan.

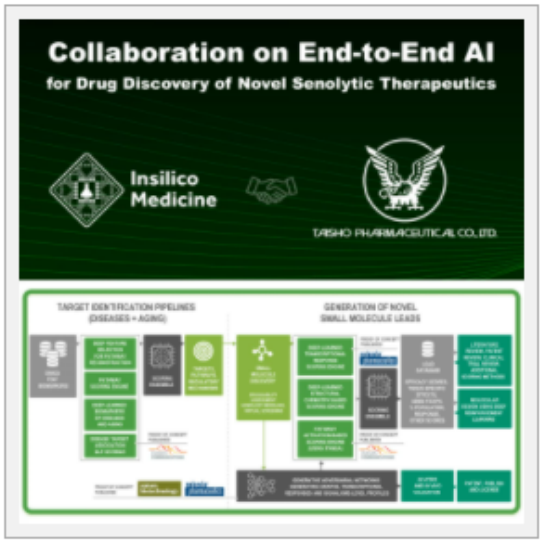


IMAGE: INSILICO PARTNERS WITH TAISHO view more ›

CREDIT: INSILICO MEDICINE

Heales
HEALTHY LIFE EXTENSION SOCIETY

British billionaire Jim Mellon plans to take his life extension start-up public in six to 12 months

PUBLISHED TUE, SEP 29 2020•5:55 AM EDT | UPDATED WED, SEP 30 2020•5:36 AM EDT

Sam Shead
@SAM_L_SHEAD

SHARE

KEY POINTS

- British billionaire Jim Mellon says he expects to take his life extension company Juvenescence public in the next six to 12 months.
- He told CNBC that Juvenescence has identified the investment banks it wants to work with.
- Juvenescence is investing in a wide range of anti-ageing therapies in the hope that one or two ideas end up working.

Photography. Rede
A look at vivo's gin
smartphone.

Aging research articles

Heales
HEALTHY LIFE EXTENSION SOCIETY

In Vivo Reprogramming Ameliorates Aging Features in Dentate Gyrus Cells and Improves Memory in Mice

Post-translational epigenetic modifications take place in mouse neurons of the dentate gyrus (DG) with age. Here, we report that age-dependent reduction in H3K9 trimethylation (H3K9me3) is prevented by cyclic induction of the Yamanaka factors used for cell reprogramming. Interestingly, Yamanaka factors elevated the levels of migrating cells containing the neurogenic markers doublecortin and calretinin, and the levels of the NMDA receptor subunit GluN2B. These changes could result in an increase in the survival of newborn DG neurons during their maturation and higher synaptic plasticity in mature neurons. Importantly, these cellular changes were accompanied by an improvement in mouse performance in the object recognition test over long time. We conclude that transient cyclic reprogramming *in vivo* in the central nervous system could be an effective strategy to ameliorate aging of the central nervous system and neurodegenerative diseases.

High-throughput small molecule screening reveals Nrf2-dependent and -independent pathways of cellular stress resistance

Aging is the dominant risk factor for most chronic diseases. Development of antiaging interventions offers the promise of preventing many such illnesses simultaneously. Cellular stress resistance is an evolutionarily conserved feature of longevity. Here, we identify compounds that induced resistance to the superoxide generator paraquat (PQ), the heavy metal cadmium (Cd), and the DNA alkylator methyl methanesulfonate (MMS). Some rescue compounds conferred resistance to a single stressor, while others provoked multiplex resistance. Induction of stress resistance in fibroblasts was predictive of longevity extension in a published large-scale longevity screen in *Caenorhabditis elegans*, although not in testing performed in worms and flies with a more restricted set of compounds. Transcriptomic analysis and genetic studies implicated Nrf2/SKN-1 signaling in stress resistance provided by two protective compounds, cardamonin and AEG 3482. Small molecules identified in this work may represent attractive tools to elucidate mechanisms of stress resistance in mammalian cells.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

Targeted senolytic prodrug is well tolerated and results in amelioration of frailty, muscle regeneration and cognitive functions in geriatric mice

Mammalian aging coincides with an accumulation of senescent cells. Depletion of senescent cells shows promise to treat age-related diseases. However, many of the senolytic drugs used to deplete senescent cells cause profound toxic side effects. Here we tested a prodrug form of a pan-cytotoxic drug and demonstrated dramatically reduced side effects in geriatric mice while gaining senolytic selectivity. Specifically, we employ a strategy that takes advantage of the greatly enriched expression of the lysosomal hydrolase β-Galactosidase in senescent cells as a tool to selectively convert the prodrug into the active parent drug. In young, old and geriatric mice this prodrug was well tolerated and proved capable of reducing the burden of senescence in multiple tissues without evident toxicity. Importantly, chronic systemic treatment of geriatric mice resulted in reduced frailty index, improved muscle tissue and stem cell functions, improved cognitive functions and overall improved survival. This work supports future senolytic prodrug designs, based on other metabolic functions characteristic of senescent cells, on different parent drugs and aimed at clinical development. This new class of senolytic prodrugs promises capabilities of targeting selectively and safely specific senescent cell types in multiple tissues to treat age-related diseases in geriatric people.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Neuropathological evaluation of a vertebrate brain aged ~ 245 years

Daniel Erny, Klara B. Jakobsdóttir & Marco Prinz

Importantly, virtually all age-related changes commonly found in elderly human brains, such as protein depositions, vascular or parenchymal calcifications were completely absent in the Greenland shark CNS. Furthermore, classical signs of neurodegeneration were not identifiable in various telencephalic regions (Fig. 1) and in the medial pallidum (Suppl. Figure 1), suggesting that the brain of vertebrates can be morphologically preserved for an extremely long time as it was described for human centenarians [13, 20].

Heales
HEALTHY LIFE EXTENSION SOCIETY

Proteomic assessment of serum biomarkers of longevity in older men

The biological bases of longevity are not well understood, and there are limited biomarkers for the prediction of long life. We used a high-throughput, discovery-based proteomics approach to identify serum peptides and proteins that were associated with the attainment of longevity in a longitudinal study of community-dwelling men age ≥65 years. Baseline serum in 1196 men were analyzed using liquid chromatography–ion mobility–mass spectrometry, and lifespan was determined during ~12 years of follow-up. Men who achieved longevity (≥90% expected survival) were compared to those who died earlier. Rigorous statistical methods that controlled for false positivity were utilized to identify 25 proteins that were associated with longevity. All these proteins were in lower abundance in long-lived men and included a variety involved in inflammation or complement activation. Lower levels of longevity-associated proteins were also associated with better health status, but as time to death shortened, levels of these proteins increased. Pathway analyses implicated a number of compounds as important upstream regulators of the proteins and implicated shared networks that underlie the observed associations with longevity. Overall, these results suggest that complex pathways, prominently including inflammation, are linked to the likelihood of attaining longevity. This work may serve to identify novel biomarkers for longevity and to understand the biology underlying lifespan.

Composition of the whole transcriptome in the human plasma: Cellular source and modification by aging

Plasma contains several bioactive molecules (RNA, DNA, proteins, lipids, and metabolites), which are well preserved in extracellular vesicles, that are involved in many types of cell-to-cell interactions, and are capable of modifying biological processes in recipient cells. To obtain information about the source of mRNA molecules present in the plasma, we analyzed the plasma extracellular RNA (exRNA) of healthy individuals using RNA-sequencing and compared it to that of the peripheral blood mononuclear cell (PBMCs) of the same individual. The resultant data indicates that large proportion of the transcripts in plasma are derived from cell types other than PBMCs. To assess aging-associated changes in the plasma exRNA composition, gene ontology enrichment analysis was performed, revealing a functional decline in biological processes as a result of aging. Additionally, plasma RNA levels were analyzed with differential expression analysis, revealing 10 transcripts with significant aging-associated changes. Thus, it seems that the plasma exRNA is not fully derived from the PBMCs. Instead, other cell types supply RNAs to constitute the plasma exRNA compartment. This was true in both the young and elderly individuals that were tested. Furthermore, the RNA content of the plasma showed significant changes due to aging, affecting important biological processes.

The Gene-Regulatory Footprint of Aging Highlights Conserved Central Regulators

Many genes and pathways have been linked to aging, yet our understanding of underlying molecular mechanisms is still lacking. Here, we measure changes in the transcriptome, histone modifications, and DNA methylome in three metabolic tissues of adult and aged mice. Transcriptome and methylome changes dominate the liver aging footprint, whereas heart and muscle globally increase chromatin accessibility, especially in aging pathways. In mouse and human data from multiple tissues and regulatory layers, age-related transcription factor expression changes and binding site enrichment converge on putative aging modulators, including ZIC1, CXXC1, HMGA1, MECP2, SREBF1, SREBF2, ETS2, ZBTB7A, and ZNF518B. Using Mendelian randomization, we establish possible epidemiological links between expression of some of these transcription factors or their targets, including CXXC1, ZNF518B, and BBC3, and longevity. We conclude that conserved modulators are at the core of the molecular footprint of aging, and variation in tissue-specific expression of some may affect human longevity.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Generation and Characterization of Anti-Glucosepane Antibodies Enabling Direct Detection of Glucosepane in Retinal Tissue

Matthew D. Streeter, Sheldon Rowan, Jason Ray, David M. McDonald, Jonathan Volkin, Jonathan Clark, Allen Taylor, and David A. Spiegel*

Although there is ample evidence that the advanced glycation end-product (AGE) glucosepane contributes to age-related morbidities and diabetic complications, the impact of glucosepane modifications on proteins has not been extensively explored due to the lack of sufficient analytical tools. Here, we report the development of the first polyclonal anti-glucosepane antibodies using a synthetic immunogen that contains the core bicyclic ring structure of glucosepane. We investigate the recognition properties of these antibodies through ELISAs involving an array of synthetic AGE derivatives and determine them to be both high-affinity and selective in binding glucosepane. We then employ these antibodies to image glucosepane in aging mouse retinae via immunohistochemistry. Our studies demonstrate for the first time accumulation of glucosepane within the retinal pigment epithelium, Bruch's membrane, and choroid: all regions of the eye impacted by age-related macular degeneration. Co-localization studies further suggest that glucosepane colocalizes with lipofuscin, which has previously been associated with lysosomal dysfunction and has been implicated in the development of age-related macular degeneration, among other diseases. We believe that the anti-glucosepane antibodies described in this study will prove highly useful for examining the role of glycation in human health and disease.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Metformin alleviates aging-associated cellular senescence of human adipose stem cells and derived adipocytes

Aging is associated with central fat redistribution, and insulin resistance. To identify age-related adipose features, we evaluated the senescence and adipogenic potential of adipose-derived-stemcells (ASCs) from abdominal subcutaneous fat obtained from healthy normal-weight young (<25y) or older women (>60y).

Aged-donor ASCs showed more intense features of aging (senescence, mitochondrial dysfunction, and oxidative stress) than young-donor ASCs. Oxidative stress and mitochondrial dysfunction occurred earlier in adipocytes derived from aged-donor than from young-donor ASCs, leading to insulin resistance and impaired adipogenesis.

When aged-donor ASCs were treated with metformin, senescence, oxidative stress and mitochondrial dysfunction returned to the levels observed in young-donor ASCs. Furthermore, metformin's prevention of senescence and dysfunction during ASC proliferation restored the cells' adipogenic capacity and insulin sensitivity. This effect was mediated by the activation of AMP-activated-protein-kinase.

We show here that targeting senescent ASCs from aged women with metformin may alleviate age-related dysfunction, insulin resistance, and impaired adipogenesis.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Metformin Use Is Associated With Slowed Cognitive Decline and Reduced Incident Dementia in Older Adults With Type 2 Diabetes: The Sydney Memory and Ageing Study

OBJECTIVE Type 2 diabetes (diabetes) is characterized by accelerated cognitive decline and higher dementia risk. Controversy exists regarding the impact of metformin, which is associated with both increased and decreased dementia rates. The objective of this study was to determine the association of metformin use with incident dementia and cognitive decline over 6 years in participants with diabetes compared with those not receiving metformin and those without diabetes.

RESEARCH DESIGN AND METHODS A prospective observational study was conducted of *N* = 1,037 community-dwelling older participants without dementia aged 70–90 years at baseline (the Sydney Memory and Ageing Study). Exclusion criteria were dementia, major neurological or psychiatric disease, or progressive malignancy. Neuropsychological testing measured cognitive function every 2 years; a battery of tests measured executive function, memory, attention/speed, language, and visuospatial function individually. These were used to determine the measure of global cognition. Incident dementia was ascertained by a multidisciplinary panel. Total brain, hippocampal, and parahippocampal volumes were measured by MRI at baseline and 2 years (*n* = 526). Data were analyzed by linear mixed modeling, including the covariates of age, sex, education, BMI, heart disease, hypertension, stroke, smoking, and apolipoprotein Eε4 carriage.

RESULTS Of *n* = 1,037, 123 had diabetes; 67 received metformin (DM+MF) and were demographically similar to those who did not (DM-noMF) and participants without diabetes (no-DM). DM+MF had significantly slower global cognition and executive function decline compared with DM-noMF. Incident dementia was significantly higher in DM-noMF compared with DM+MF (odds ratio 5.29 [95% CI 1.17–23.88]; *P* = 0.05).

CONCLUSIONS Older people with diabetes receiving metformin have slower cognitive decline and lower dementia risk. Large randomized studies in people with and without diabetes will determine whether these associations can be attributed to metformin.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Metformin rescues Parkinson's disease phenotypes caused by hyperactive mitochondria

Metabolic dysfunction occurs in many age-related neurodegenerative diseases, yet its role in disease etiology remains poorly understood. We recently discovered a potential causal link between the branched-chain amino acid transferase *BCAT-1* and the neurodegenerative movement disorder Parkinson's disease (PD). RNAi-mediated knockdown of *Caenorhabditis elegans bcat-1* is known to recapitulate PD-like features, including progressive motor deficits and neurodegeneration with age, yet the underlying mechanisms have remained unknown. Using transcriptomic, metabolomic, and imaging approaches, we show here that *bcat-1* knockdown increases mitochondrial respiration and induces oxidative damage in neurons through mammalian target of rapamycin-independent mechanisms. Increased mitochondrial respiration, or "mitochondrial hyperactivity," is required for *bcat-1(RNAi)* neurotoxicity. Moreover, we show that post–disease-onset administration of the type 2 diabetes medication metformin reduces mitochondrial respiration to control levels and significantly improves both motor function and neuronal viability. Taken together, our findings suggest that mitochondrial hyperactivity may be an early event in the pathogenesis of PD, and that strategies aimed at reducing mitochondrial respiration may constitute a surprising new avenue for PD treatment.

Acarbose has sex-dependent and independent effects on age-related physical function, cardiac health and lipid biology

With an expanding aging population burdened with comorbidities, there is considerable interest in treatments that optimize health in later life. Acarbose (ACA), a drug used clinically to treat Type 2 diabetes (T2DM) can extend mouse lifespan, with greater effect in males than in females. Utilizing a genetically heterogeneous mouse model, we tested the ability of ACA to ameliorate functional, pathological and biochemical changes that occur during aging, and determined which of the effects of age and drug were sex-dependent. In both sexes, ACA prevented age-dependent loss of body mass, in addition to improving balance/coordination on an accelerating rotarod, rotarod endurance, and grip strength. Age-related cardiac hypertrophy was seen only in male mice, and this male-specific aging effect was attenuated by ACA. ACA-sensitive cardiac changes were associated with reduced activation of cardiac growth promoting pathways and increased abundance of peroxisomal proteins involved in lipid metabolism. ACA further ameliorated age-associated changes in cardiac lipid species, particularly lysophospholipids – changes which have previously been associated with aging, cardiac dysfunction and cardiovascular disease in humans. In the liver, ACA had pronounced effects on lipid handling in both sexes, reducing hepatic lipidosis during aging and shifting the liver lipidome in adulthood, particularly favoring reduced triglyceride (TAG) accumulation. Our results demonstrate that ACA, already in clinical use for T2DM, has broad-ranging anti-aging effects in multiple tissues, and may have the potential to increase physical function and alter lipid biology to preserve or improve health at older ages.

Heales
HEALTHY LIFE EXTENSION SOCIETY

SIRT1 is downregulated by autophagy in senescence and ageing

SIRT1 (Sir2) is an NAD^+-dependent deacetylase that plays critical roles in a broad range of biological events, including metabolism, the immune response and ageing[1,2,3,4,5]. Although there is strong interest in stimulating SIRT1 catalytic activity, the homeostasis of SIRT1 at the protein level is poorly understood. Here we report that macroautophagy (hereafter referred to as autophagy), a catabolic membrane trafficking pathway that degrades cellular components through autophagosomes and lysosomes, mediates the downregulation of mammalian SIRT1 protein during senescence and in vivo ageing. In senescence, nuclear SIRT1 is recognized as an autophagy substrate and is subjected to cytoplasmic autophagosome–lysosome degradation, via the autophagy protein LC3. Importantly, the autophagy–lysosome pathway contributes to the loss of SIRT1 during ageing of several tissues related to the immune and haematopoietic system in mice, including the spleen, thymus, and haematopoietic stem and progenitor cells, as well as in $CD8^+CD28^-$ T cells from aged human donors. Our study reveals a mechanism in the regulation of the protein homeostasis of SIRT1 and suggests a potential strategy to stabilize SIRT1 to promote productive ageing.

Heales
HEALTHY LIFE EXTENSION SOCIETY

PREPRINT

NAD+ flux is maintained in aged mice

NAD$^+$ is an essential coenzyme found in all living cells. NAD$^+$ concentrations decline during aging, but whether this reflects impaired production or accelerated consumption remains unclear. Here we employed isotope tracing and mass spectrometry to probe NAD$^+$ metabolism across tissues in aged mice. In 25-month-old mice, we observe modest tissue NAD$^+$ depletion (median decrease ~ 30%) without significant changes in circulating NAD$^+$ precursors. Isotope tracing showed unimpaired synthesis of circulating nicotinamide from tryptophan, and maintained flux of circulating nicotinamide into tissue NAD$^+$ pools. Although absolute NAD$^+$ biosynthetic flux was maintained in most tissues of aged mice, fractional tissue NAD$^+$ labeling from infused labeled nicotinamide was modestly accelerated, consistent with increased activity of NAD$^+$ consuming enzymes. Long-term calorie restriction partially mitigated age-associated NAD$^+$ decline despite decreasing NAD$^+$ synthesis, suggesting that calorie restriction reduces NAD$^+$ consumption. Thus, age-related decline in NAD$^+$ is relatively subtle and driven by increased NAD$^+$ consumer activity rather than impaired production.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Kinetic fingerprints differentiate the mechanisms of action of anti-Aβ antibodies

The amyloid cascade hypothesis, according to which the self-assembly of amyloid-β peptide (Aβ) is a causative process in Alzheimer's disease, has driven many therapeutic efforts for the past 20 years. Failures of clinical trials investigating Aβ-targeted therapies have been interpreted as evidence against this hypothesis, irrespective of the characteristics and mechanisms of action of the therapeutic agents, which are highly challenging to assess. Here, we combine kinetic analyses with quantitative binding measurements to address the mechanism of action of four clinical stage anti-Aβ antibodies, aducanumab, gantenerumab, bapineuzumab and solanezumab. We quantify the influence of these antibodies on the aggregation kinetics and on the production of oligomeric aggregates and link these effects to the affinity and stoichiometry of each antibody for monomeric and fibrillar forms of Aβ. Our results reveal that, uniquely among these four antibodies, aducanumab dramatically reduces the flux of Aβ oligomers.

C. elegans aging research

NemaLife chip: a micropillar-based microfluidic culture device optimized for aging studies in crawling C. elegans

In this study, we report a microfluidic device for the whole-life culture of the nematode Caenorhabditis elegans that allows the scoring of animal survival and health measures. This device referred to as the NemaLife chip features: (1) an optimized micropillar arena in which animals can crawl, (2) sieve channels that separate progeny and prevent the loss of adults from the arena during culture maintenance, and (3) ports that allow rapid accessibility for feeding the adult-only population and introducing reagents as needed. The pillar arena geometry was optimized to accommodate the growing body size during culture and emulate the body gait and locomotion of animals reared on agar. Likewise, feeding protocols were optimized to recapitulate longevity outcomes typical of standard plate growth. Key benefits of the NemaLife Chip include eliminating the need to perform repeated manual transfers of adults during survival assays, negating the need for progeny-blocking chemical interventions, and avoiding the swim-induced stress across lifespan in animals reared in liquid. We also show that the culture of animals in pillar-less microfluidic chambers reduces lifespan and introduces physiological stress by increasing the occurrence of age-related vulval integrity disorder. We validated our pillar-based device with longevity analyses of classical aging mutants (daf-2, age-1, eat-2, and daf-16) and animals subjected to RNAi knockdown of age-related genes (age-1 and daf-16). We also showed that healthspan measures such as pharyngeal pumping and tap-induced stimulated reversals can be scored across the lifespan in the NemaLife chip. Overall, the capacity to generate reliable lifespan and physiological data underscores the potential of the NemaLife chip to accelerate healthspan and lifespan investigations in C. elegans.

Heales
HEALTHY LIFE EXTENSION SOCIETY

SUMO promotes longevity and maintains mitochondrial homeostasis during ageing in *Caenorhabditis elegans*

The insulin/IGF signalling pathway impacts lifespan across distant taxa, by controlling the activity of nodal transcription factors. In the nematode *Caenorhabditis elegans*, the transcription regulators DAF-16/FOXO and SKN-1/Nrf function to promote longevity under conditions of low insulin/IGF signalling and stress. The activity and subcellular localization of both DAF-16 and SKN-1 is further modulated by specific posttranslational modifications, such as phosphorylation and ubiquitination. Here, we show that ageing elicits a marked increase of SUMO levels in *C. elegans*. In turn, SUMO fine-tunes DAF-16 and SKN-1 activity in specific *C. elegans* somatic tissues, to enhance stress resistance. SUMOylation of DAF-16 modulates mitochondrial homeostasis by interfering with mitochondrial dynamics and mitophagy. Our findings reveal that SUMO is an important determinant of lifespan, and provide novel insight, relevant to the complexity of the signalling mechanisms that influence gene expression to govern organismal survival in metazoans.

REVIEWS/COMMENTS/ METHODS/EDITORIALS

Heales
HEALTHY LIFE EXTENSION SOCIETY

Targeting Senescent Cells for a Healthier Aging: Challenges and Opportunities

Aging is a physiological decline in both structural homeostasis and functional integrity, progressively affecting organismal health. A major hallmark of aging is the accumulation of senescent cells, which have entered a state of irreversible cell cycle arrest after experiencing inherent or environmental stresses. Although cellular senescence is essential in several physiological events, it plays a detrimental role in a large array of age-related pathologies. Recent biomedical advances in specifically targeting senescent cells to improve healthy aging, or alternatively, postpone natural aging and age-related diseases, a strategy termed senotherapy, have attracted substantial interest in both scientific and medical communities. Challenges for aging research are highlighted and potential avenues that can be leveraged for therapeutic interventions to control aging and age-related disorders in the current era of precision medicine.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Promising biomarkers of human aging: In search of a multi-omics panel to understand the aging process from a multidimensional perspective

The aging process has been linked to the occurrence of chronic diseases and functional impairments, including cancer, sarcopenia, frailty, metabolic, cardiovascular, and neurodegenerative diseases. Nonetheless, aging is highly variable and heterogeneous and represents a challenge for its characterization. In this sense, *intrinsic capacity* (IC) stands as a novel perspective by the World Health Organization, which integrates the individual wellbeing, environment, and risk factors to understand aging. However, there is a lack of quantitative and qualitative attributes to define it objectively. Therefore, in this review we attempt to summarize the most relevant and promising biomarkers described in clinical studies at date over different molecular levels, including epigenomics, transcriptomics, proteomics, metabolomics, and the microbiome. To aid gerontologists, geriatricians, and biomedical researchers to understand the aging process through the *IC*. Aging biomarkers reflect the physiological state of individuals and the underlying mechanisms related to homeostatic changes throughout an individual lifespan; they demonstrated that aging could be measured independently of time (that may explain its heterogeneity) and to be helpful to predict age-related syndromes and mortality. In summary, we highlight the areas of opportunity and gaps of knowledge that must be addressed to fully integrate biomedical findings into clinically useful tools and interventions.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Targeting metabolic pathways for extension of lifespan and healthspan across multiple species

Metabolism plays a significant role in the regulation of aging at different levels, and metabolic reprogramming represents a major driving force in aging. Metabolic reprogramming leads to impaired organismal fitness, an age-dependent increase in susceptibility to diseases, decreased ability to mount a stress response, and increased frailty. The complexity of age-dependent metabolic reprogramming comes from the multitude of levels on which metabolic changes can be connected to aging and regulation of lifespan. This is further complicated by the different metabolic requirements of various tissues, cross-organ communication via metabolite secretion, and direct effects of metabolites on epigenetic state and redox regulation; however, not all of these changes are causative to aging. Studies in yeast, flies, worms, and mice have played a crucial role in identifying mechanistic links between observed changes in various metabolic traits and their effects on lifespan. Here, we review how changes in the organismal and organ-specific metabolome are associated with aging and how targeting of any one of over a hundred different targets in specific metabolic pathways can extend lifespan. An important corollary is that restriction or supplementation of different metabolites can change activity of these metabolic pathways in ways that improve healthspan and extend lifespan in different organisms. Due to the high levels of conservation of metabolism in general, translating findings from model systems to human beings will allow for the development of effective strategies for human health- and lifespan extension.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Translational control in the naked mole-rat as a model highly resistant to cancer

Dysregulation of mRNA translation is involved in the onset and progression of different types of cancer. To gain insight into novel genetic strategies to avoid this malady, we reviewed the available genomic, transcriptomic, and proteomic data about the translational machinery from the naked-mole rat (NMR) *Heterocephalus glaber*, a new model of study that exhibits high resistance to cancer. The principal features that might confer cancer resistance are 28S rRNA fragmentation, RPL26 and eIF4G overexpression, global downregulation of mTOR pathway, specific amino acid residues in RAPTOR (P908) and RICTOR (V1695), and the absence of 4E-BP3. These features are not only associated with cancer but also might couple longevity and adaptation to hypoxia. We propose that the regulation of translation is among the strategies endowing NMR cancer resistance.

Branched chain amino acids, aging and age-related health

Branched chain amino acids (BCAA: leucine, valine, isoleucine) have key physiological roles in the regulation of protein synthesis, metabolism, food intake and aging. Many studies report apparently inconsistent conclusions about the relationships between blood levels of BCAAs or dietary manipulation of BCAAs with age-related changes in body composition, sarcopenia, obesity, insulin and glucose metabolism, and aging biology itself. These divergent results can be resolved by consideration of the role of BCAAs as signalling molecules and the bidirectional mechanistic relationship between BCAAs and some aging phenotypes. The effects of BCAAs are also influenced by the background nutritional composition such as macronutrient ratios and imbalance with other amino acids. Understanding the interaction between BCAAs and other components of the diet may provide new opportunities for influencing age-related outcomes through manipulation of dietary BCAAs together with titration of macronutrient ratios and other amino acids.

Brain arteriolosclerosis

Brain arteriolosclerosis (B-ASC), characterized by pathologic arteriolar wall thickening, is a common finding at autopsy in aged persons and is associated with cognitive impairment. Hypertension and diabetes are widely recognized as risk factors for B-ASC. Recent research indicates other and more complex risk factors and pathogenetic mechanisms. Here, we describe aspects of the unique architecture of brain arterioles, histomorphologic features of B-ASC, relevant neuroimaging findings, epidemiology and association with aging, established genetic risk factors, and the co-occurrence of B-ASC with other neuropathologic conditions such as Alzheimer's disease and limbic-predominant age-related TDP-43 encephalopathy (LATE). There may also be complex physiologic interactions between metabolic syndrome (e.g., hypertension and inflammation) and brain arteriolar pathology. Although there is no universally applied diagnostic methodology, several classification schemes and neuroimaging techniques are used to diagnose and categorize cerebral small vessel disease pathologies that include B-ASC, microinfarcts, microbleeds, lacunar infarcts, and cerebral amyloid angiopathy (CAA). In clinical-pathologic studies that factored in comorbid diseases, B-ASC was independently associated with impairments of global cognition, episodic memory, working memory, and perceptual speed, and has been linked to autonomic dysfunction and motor symptoms including parkinsonism. We conclude by discussing critical knowledge gaps related to B-ASC and suggest that there are probably subcategories of B-ASC that differ in pathogenesis. Observed in over 80% of autopsied individuals beyond 80 years of age, B-ASC is a complex and under-studied contributor to neurologic disability.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Effect of rapamycin on aging and age-related diseases—past and future

Ramasamy Selvarani, Sabira Mohammed & Arlan Richardson

In 2009, rapamycin was reported to increase the lifespan of mice when implemented later in life. This observation resulted in a sea-change in how researchers viewed aging. This was the first evidence that a pharmacological agent could have an impact on aging when administered later in life, i.e., an intervention that did not have to be implemented early in life before the negative impact of aging. Over the past decade, there has been an explosion in the number of reports studying the effect of rapamycin on various diseases, physiological functions, and biochemical processes in mice. In this review, we focus on those areas in which there is strong evidence for rapamycin's effect on aging and age-related diseases in mice, e.g., lifespan, cardiac disease/function, central nervous system, immune system, and cell senescence. We conclude that it is time that pre-clinical studies be focused on taking rapamycin to the clinic, e.g., as a potential treatment for Alzheimer's disease.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Autophagy in Human Diseases

Noboru Mizushima, M.D., Ph.D., and Beth Levine, M.D.

Autophagy is a complex process of intracellular degradation of senescent or malfunctioning organelles. Dysregulated autophagy is associated with certain cancers, neurodegenerative diseases, immune dysfunction, and aging. Therapies aimed at regulating autophagy are being developed.

OTHER RESEARCH & REVIEWS

Heales
HEALTHY LIFE EXTENSION SOCIETY

A Quantitative Proteome Map of the Human Body

Determining protein levels in each tissue and how they compare with RNA levels is important for understanding human biology and disease as well as regulatory processes that control protein levels. We quantified the relative protein levels from over 12,000 genes across 32 normal human tissues. Tissue-specific or tissue-enriched proteins were identified and compared to transcriptome data. Many ubiquitous transcripts are found to encode tissue-specific proteins. Discordance of RNA and protein enrichment revealed potential sites of synthesis and action of secreted proteins. The tissue-specific distribution of proteins also provides an in-depth view of complex biological events that require the interplay of multiple tissues. Most importantly, our study demonstrated that protein tissue-enrichment information can explain phenotypes of genetic diseases, which cannot be obtained by transcript information alone. Overall, our results demonstrate how understanding protein levels can provide insights into regulation, secretome, metabolism, and human diseases.