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Scientific News
3rd of May 2020
Sven Bulterijs

Business/Conferences/ General news

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Intrado GlobeNewswire

BioAge Signs Exclusive License Agreement with Taisho to Develop and Commercialize Taisho's Phase 1 HIF-PH Inhibitor to Treat Aging

BioAge's proprietary platform of human aging data demonstrates that the Hypoxia-inducible factor (HIF) pathway is linked to healthspan and lifespan

April 29, 2020 22:00 ET | **Source:** BioAge Labs, Inc.

RICHMOND, Calif., April 29, 2020 (GLOBE NEWSWIRE) -- BioAge Labs, Inc., a biotechnology company developing medicines to treat aging and age-related diseases, today announced that it has entered into an exclusive worldwide license agreement with Taisho Pharmaceutical Co., Ltd. [Head Office: Toshima-ku, Tokyo, President: Shigeru Uehara] ("Taisho") to develop and commercialize Taisho's clinical-stage Hypoxia-inducible factor-prolyl hydroxylase (HIF-PH) inhibitor, BGE-117 (named TS-143 by Taisho), to ameliorate multiple diseases of aging.

"This is a significant milestone for BioAge that enables us to initiate our first clinical trial of BGE-117 to evaluate the impact of HIF activation on several measures of aging in elderly patients. Our proprietary human data platform shows that HIF signaling is a key longevity pathway that drives regeneration, healing and resilience," said Kristen Fortney, PhD, BioAge's Chief Executive Officer. "BioAge's AI-driven platform is built on longitudinal human aging samples with multi-omics phenotyping and has revealed multiple pathways and mechanisms where we can intervene to positively impact human healthspan and lifespan. BGE-117 is the first of several promising therapies that we plan to bring forward to treat diseases of aging."

Under the terms of the agreement, BioAge will make an upfront payment to Taisho, who is entitled to receive development and commercial milestone payments plus royalties based on annual net sales. BioAge will be responsible for all development, manufacturing and commercialization of BGE-117 worldwide while Taisho has an option right for co-commercialization in Japan and several countries in Southeast Asia.

The Hypoxia-inducible factor (HIF) pathway is linked to healthspan and lifespan in BioAge's proprietary human aging data. Pathway activation levels are significantly associated with longevity and multiple functional measures. The Company believes that BGE-117 can potentially treat multiple diseases of aging through the activation of HIF-1 target genes that are involved in numerous biological processes including tissue regeneration, erythropoiesis, glycolysis, glucose uptake, vascular remodeling and angiogenesis. Inhibition of HIF-PH increases HIF pathway activation and has the potential to increase resilience, repair and regeneration across multiple body systems.

BGE-117 is a potent, orally administered small molecule inhibitor of HIF-PH demonstrating early clinical activity and safety in a Phase 1 study in healthy volunteers and a Phase 1 study in non-dialysis and hemodialysis patients with chronic kidney disease.[1] HIF-PH inhibitors are an emerging class of compounds that have been demonstrated to be safe and well-tolerated in over 20,000 subjects in clinical trials.

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Boehringer Ingelheim taps Insilico Medicine for AI drug target collaboration

by Conor Hale | Apr 14, 2020 6:00pm

The recent FierceMedTech Fierce 15 winner will provide Boehringer Ingelheim with additional artificial intelligence capabilities and its Pandomics Discovery Platform to help visualize data on cell signaling pathways and disease profiles. (Boehringer Ingelheim)

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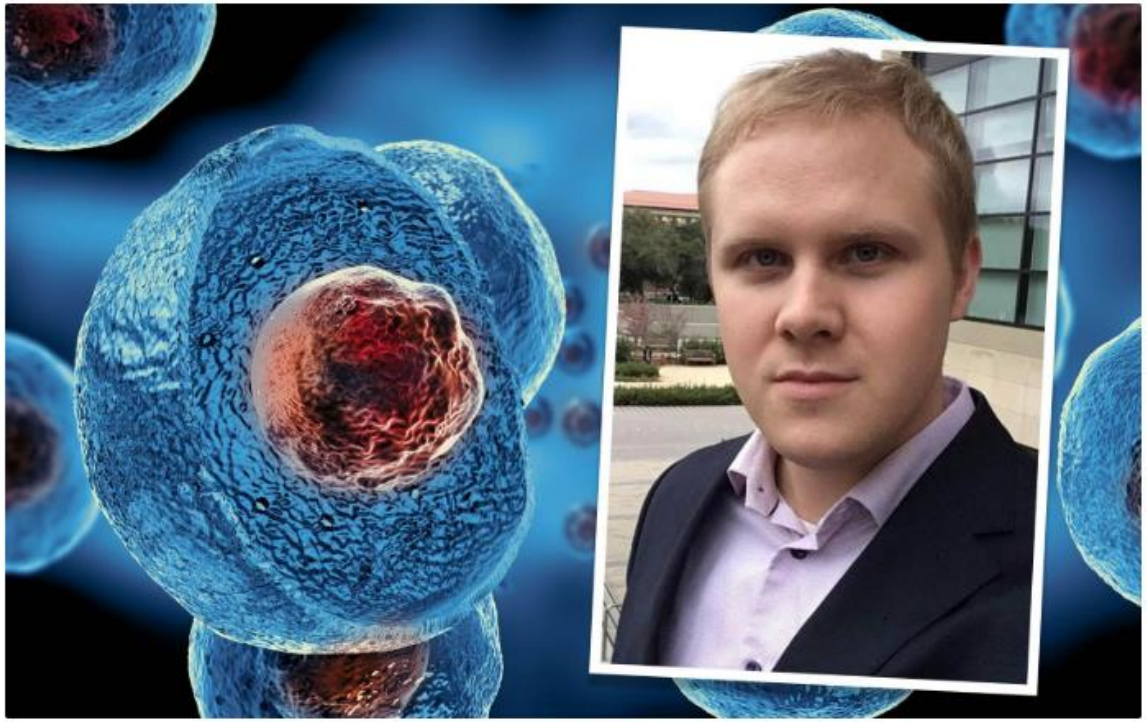
CORONAVIRUS

To crack future pandemics, crack the mystery of aging

A relatively new area of research is about trying to slow down aging and, by extension, even be able to rejuvenate people. Now the field is getting even more attention because of the coronavirus pandemic.

MAGNUS ASCHAN
16 APR 2020 • 6 MIN READ



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COVID-19 is an emergent disease of aging

Didac Santesmasses, José Pedro Castro, Aleksandr A Zenin, Anastasia V Shindyapina, Maxim V Gerashchenko, Bohan Zhang, Csaba Kerepesi, Sun Hee Yim, Peter O Fedichev, Vadim N Gladyshev

doi: https://doi.org/10.1101/2020.04.15.20060095

This article is a preprint and has not been peer-reviewed [what does this mean?]. It reports new medical research that has yet to be evaluated and so should *not* be used to guide clinical practice.

Abstract

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 highly contagious and often leads to severe viral pneumonia with respiratory failure and death in the elderly and subjects 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 Italy, Spain, South Korea, and China, 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 therapeutic approaches that affect specific pathways, by approaches that target the aging process.

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A geroscience perspective on COVID-19 mortality FREE

Daniel E L Promislow, D.Phil

The Journals of Gerontology: Series A, glaa094, https://doi.org/10.1093/gerona/glaa094
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Abstract

A novel coronavirus, SARS-CoV-2, emerged in December 2019, leading within a few months to a global pandemic. COVID-19, the disease caused by this highly contagious virus, can have serious health consequences, though risks of complications are highly age-dependent. Rates of hospitalization and death are less than 0.1% in children, but increase to 10% or more in older people. Moreover, at all ages, men are more likely than women to suffer serious consequences from COVID-19. These patterns are familiar to the geroscience community. The effects of age and sex on mortality rates from COVID-19 mirror the effects of aging on almost all major causes of mortality. These similarities are explored here, and underscore the need to consider the role of basic biological mechanisms of aging on potential treatment and outcomes of COVID-19.

Rejuvenation Research, Vol. 23, No. 2 | Editorial

Being Rational About Health: The Pandemic's Long-Term Silver Lining?

Aubrey D.N.J. de Grey

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Generals are always prepared to fight the last war.

—Winston Churchill

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Geroprotective and senoremediative strategies to reduce the comorbidity, infection rates, severity, and lethality in gerophilic and gerolavic infections

The recently identified SARS-CoV-2 betacoronavirus responsible for the COVID-19 pandemic has uncovered the age-associated vulnerability in the burden of disease and put aging research in the spotlight. The limited data available indicates that COVID-19 should be referred to as a gerolavic (from Greek, géros "old man" and epilavís, "harmful") infection because the infection rates, severity, and lethality are substantially higher in the population aged 60 and older. This is primarily due to comorbidity but may be partially due to immunosenescence, decreased immune function in the elderly, and general loss of function, fitness, and increased frailty associated with aging. Immunosenescence is a major factor affecting vaccination response, as well as the severity and lethality of infectious diseases. While vaccination reduces infection rates, and therapeutic interventions reduce the severity and lethality of infections, these interventions have limitations. Previous studies showed that postulated geroprotectors, such as sirolimus (rapamycin) and its close derivative rapalog everolimus (RAD001), decreased infection rates in a small sample of elderly patients. This article presents a review of the limited literature available on geroprotective and senoremediative interventions that may be investigated to decrease the disease burden of gerolavic infections. This article also highlights a need for rigorous clinical validation of deep aging clocks as surrogate markers of biological age. These could be used to assess the need for, and efficacy of, geroprotective and senoremediative interventions and provide better protection for elderly populations from gerolavic infections. This article does not represent medical advice and the medications described are not yet licensed or recommended as immune system boosters, as they have not undergone clinical evaluation for this purpose.

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How does coronavirus kill? Clinicians trace a ferocious rampage through the body, from brain to toes

By Meredith Wadman, Jennifer Couzin-Frankel, Jocelyn Kaiser, Catherine Matacic | Apr. 17, 2020 , 6:45 PM

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

On rounds in a 20-bed intensive care unit one recent day, physician Joshua Denson assessed two patients with seizures, many with respiratory failure and others whose kidneys were on a dangerous downhill slide. Days earlier, his rounds had been interrupted as his team tried, and failed, to resuscitate a young woman whose heart had stopped. All shared one thing, says Denson, a pulmonary and critical care physician at the Tulane University School of Medicine. "They are all COVID positive."

As the number of confirmed cases of COVID-19 surges past 2.2 million globally and deaths surpass 150,000, clinicians and pathologists are struggling to understand the damage wrought by the coronavirus as it tears through the body. They are realizing that although the lungs are ground zero, its reach can extend to many organs including the heart and blood vessels, kidneys, gut, and brain.

"[The disease] can attack almost anything in the body with devastating consequences," says cardiologist Harlan Krumholz of Yale University and Yale-New Haven Hospital, who is leading multiple efforts to gather clinical data on COVID-19. "Its ferocity is breathtaking and humbling."

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Gilead's remdesivir scores emergency FDA nod in COVID-19 days after big data reveal

by Eric Sagonowsky | May 1, 2020 3:48pm

Gilead's remdesivir scored an FDA emergency use authorization in COVID-19. (Gilead China)

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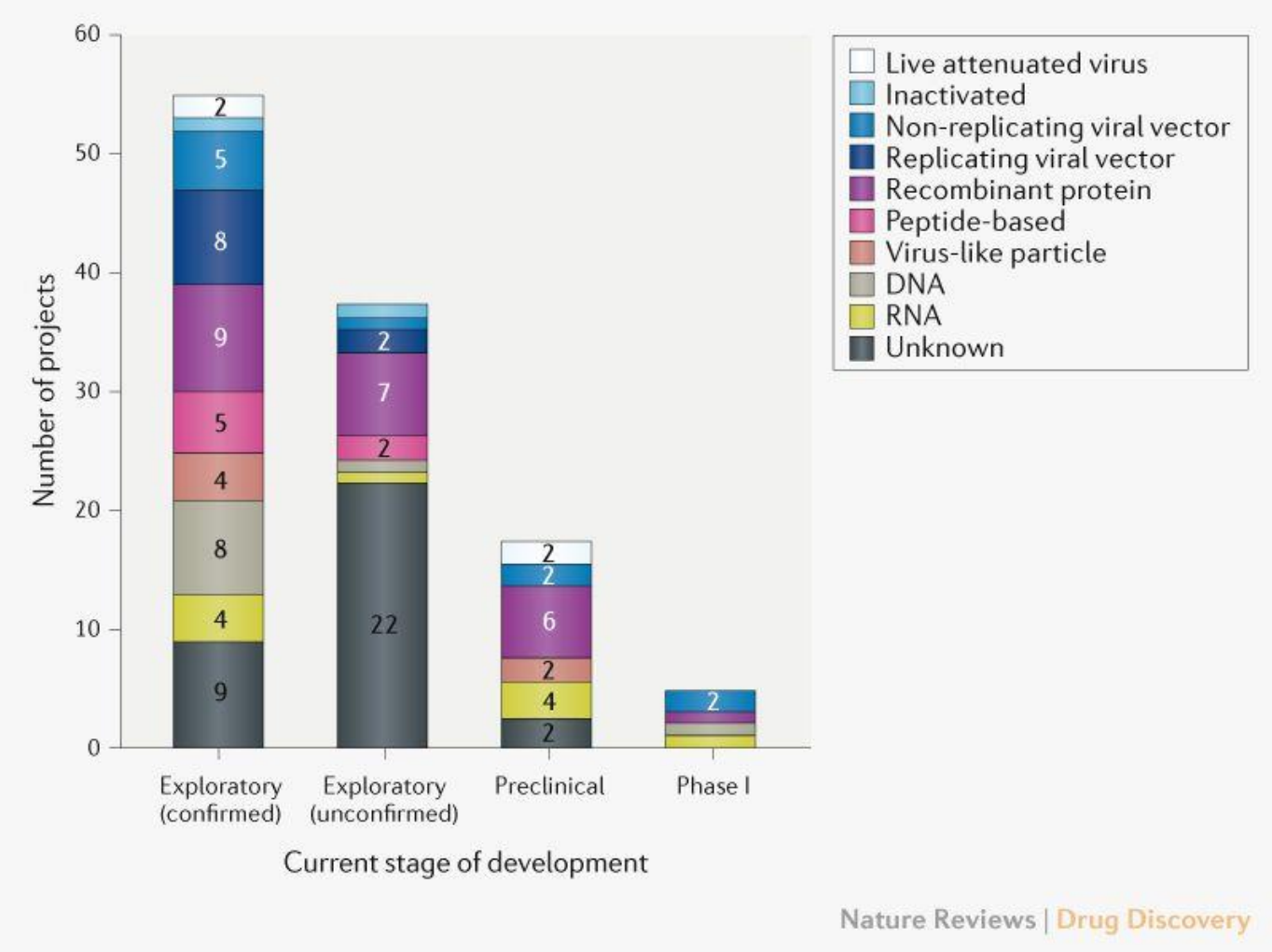
FROM THE ANALYST'S COUCH · 09 APRIL 2020

The COVID-19 vaccine development landscape

Tung Thanh Le, Zacharias Andreadakis, Arun Kumar, Raúl Gómez Román, Stig Tollefsen, Melanie Saville & Stephen Mayhew



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In Race for a Coronavirus Vaccine, an Oxford Group Leaps Ahead

As scientists at the Jenner Institute prepare for mass clinical trials, new tests show their vaccine to be effective in monkeys.

Prof. Adrian Hill, the Jenner Institute's director, in Oxford on Friday. His team is working to produce a coronavirus vaccine. Mary Turner for The New York Times

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Clinical trials on drug repositioning for COVID-19 treatment

Sandro G. Viveiros Rosa[1] and Wilson C. Santos[1]

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ABSTRACT

Go to:

The World Health Organization (WHO) was informed on December 2019 about a coronavirus pneumonia outbreak in Wuhan, Hubei province (China). Subsequently, on March 12, 2020, 125,048 cases and 4,614 deaths were reported. Coronavirus is an enveloped RNA virus, from the genus *Betacoronavirus*, that is distributed in birds, humans, and other mammals. WHO has named the novel coronavirus disease as COVID-19. More than 80 clinical trials have been launched to test coronavirus treatment, including some drug repurposing or repositioning for COVID-19. Hence, we performed a search in March 2020 of the clinicaltrials.gov database. The eligibility criteria for the retrieved studies were: contain a clinicaltrials.gov base identifier number; describe the number of participants and the period for the study; describe the participants' clinical conditions; and utilize interventions with medicines already studied or approved for any other disease in patients infected with the novel coronavirus SARS-CoV-2 (2019-nCoV). It is essential to emphasize that this article only captured trials listed in the clinicaltrials.gov database. We identified 24 clinical trials, involving more than 20 medicines, such as human immunoglobulin, interferons, chloroquine, hydroxychloroquine, arbidol, remdesivir, favipiravir, lopinavir, ritonavir, oseltamivir, methylprednisolone, bevacizumab, and traditional Chinese medicines (TCM). Although drug repurposing has some limitations, repositioning clinical trials may represent an attractive strategy because they facilitate the discovery of new classes of medicines; they have lower costs and take less time to reach the market; and there are existing pharmaceutical supply chains for formulation and distribution.

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Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19)

A Review

James M. Sanders, PhD, PharmD[1,2]; Marguerite L. Monogue, PharmD[1,2]; Tomasz Z. Jodlowski, PharmD[3]; et al

» Author Affiliations | Article Information

JAMA. Published online April 13, 2020. doi:10.1001/jama.2020.6019

Related Articles

Abstract

Importance The pandemic of coronavirus disease 2019 (COVID-19) caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) presents an unprecedented challenge to identify effective drugs for prevention and treatment. Given the rapid pace of scientific discovery and clinical data generated by the large number of people rapidly infected by SARS-CoV-2, clinicians need accurate evidence regarding effective medical treatments for this infection.

Observations No proven effective therapies for this virus currently exist. The rapidly expanding knowledge regarding SARS-CoV-2 virology provides a significant number of potential drug targets. The most promising therapy is remdesivir. Remdesivir has potent in vitro activity against SARS-CoV-2, but it is not US Food and Drug Administration approved and currently is being tested in ongoing randomized trials. Oseltamivir has not been shown to have efficacy, and corticosteroids are currently not recommended. Current clinical evidence does not support stopping angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in patients with COVID-19.

Conclusions and Relevance The COVID-19 pandemic represents the greatest global public health crisis of this generation and, potentially, since the pandemic influenza outbreak of 1918. The speed and volume of clinical trials launched to investigate potential therapies for COVID-19 highlight both the need and capability to produce high-quality evidence even in the middle of a pandemic. No therapies have been shown effective to date.

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Medical masks vs N95 respirators for preventing COVID-19 in healthcare workers: A systematic review and meta-analysis of randomized trials

Data Synthesis

Four RCTs were meta-analyzed adjusting for clustering. Compared with N95 respirators; the use of medical masks did not increase laboratory-confirmed viral (including coronaviruses) respiratory infection (OR 1.06; 95% CI 0.90-1.25; I^2 = 0%; low certainty in the evidence) or clinical respiratory illness (OR 1.49; 95% CI: 0.98-2.28; I^2 = 78%; very low certainty in the evidence). Only one trial evaluated coronaviruses separately and found no difference between the two groups (P = .49).

Limitations

Indirectness and imprecision of available evidence.

Conclusions

Low certainty evidence suggests that medical masks and N95 respirators offer similar protection against viral respiratory infection including coronavirus in healthcare workers during non–aerosol-generating care. Preservation of N95 respirators for high-risk, aerosol-generating procedures in this pandemic should be considered when in short supply.

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Assessment of N95 respirator decontamination and re-use for SARS-CoV-2

Robert Fischer, Dylan H Morris, Neeltje van Doremalen, Shanda Sarchette, Jeremiah Matson, Trenton Bushmaker, Claude Kwe Yinda, Stephanie Seifert, Amandine Gamble, Brandi Williamson, Seth Judson, Emmie de Wit, Jamie Lloyd-Smith, Vincent Munster

The unprecedented pandemic of SARS-CoV-2 has created worldwide shortages of personal protective equipment, in particular respiratory protection such as N95 respirators. SARS-CoV-2 transmission is frequently occurring in hospital settings, with numerous reported cases of nosocomial transmission highlighting the vulnerability of healthcare workers. In general, N95 respirators are designed for single use prior to disposal. Here, we have analyzed four readily available and often used decontamination methods: UV, 70% ethanol, 70C heat and vaporized hydrogen peroxide for inactivation of SARS-CoV-2 on N95 respirators. Equally important we assessed the function of the N95 respirators after multiple wear and decontamination

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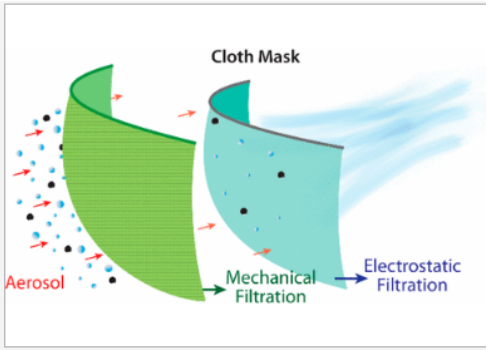
Aerosol Filtration Efficiency of Common Fabrics Used in Respiratory Cloth Masks

Abhiteja Konda, Abhinav Prakash, Gregory A. Moss, Michael Schmoldt, Gregory D. Grant and Supratik Guha*

The emergence of a pandemic affecting the respiratory system can result in a significant demand for face masks. This includes the use of cloth masks by large sections of the public, as can be seen during the current global spread of COVID-19. However, there is limited knowledge available on the performance of various commonly available fabrics used in cloth masks. Importantly, there is a need to evaluate filtration efficiencies as a function of aerosol particulate sizes in the 10 nm to 10 μm range, which is particularly relevant for respiratory virus transmission. We have carried out these studies for several common fabrics including cotton, silk, chiffon, flannel, various synthetics, and their combinations. Although the filtration efficiencies for various fabrics when a single layer was used ranged from 5 to 80% and 5 to 95% for particle sizes of <300 nm and >300 nm, respectively, the efficiencies improved when multiple layers were used and when using a specific combination of different fabrics. Filtration efficiencies of the hybrids (such as cotton–silk, cotton–chiffon, cotton–flannel) was >80% (for particles <300 nm) and >90% (for particles >300 nm). We speculate that the enhanced performance of the hybrids is likely due to the combined effect of mechanical and electrostatic-based filtration. Cotton, the most widely used material for cloth masks performs better at higher weave densities (*i.e.*, thread count) and can make a significant difference in filtration efficiencies. Our studies also imply that gaps (as caused by an improper fit of the mask) can result in over a 60% decrease in the filtration efficiency, implying the need for future cloth mask design studies to take into account issues of "fit" and leakage, while allowing the exhaled air to vent efficiently. Overall, we find that combinations of various commonly available fabrics used in cloth masks can potentially provide significant protection against the transmission of aerosol particles.



Aging research articles

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Elimination of senescent cells by β-galactosidase-targeted prodrug attenuates inflammation and restores physical function in aged mice

Cellular senescence, a persistent state of cell cycle arrest, accumulates in aged organisms, contributes to tissue dysfunction, and drives age-related phenotypes. The clearance of senescent cells is expected to decrease chronic, low-grade inflammation and improve tissue repair capacity, thus attenuating the decline of physical function in aged organisms. However, selective and effective clearance of senescent cells of different cell types has proven challenging. Herein, we developed a prodrug strategy to design a new compound based on the increased activity of lysosomal β-galactosidase (β-gal), a primary characteristic of senescent cells. Our prodrug SSK1 is specifically activated by β-gal and eliminates mouse and human senescent cells independently of senescence inducers and cell types. In aged mice, our compound effectively cleared senescent cells in different tissues, decreased the senescence- and age-associated gene signatures, attenuated low-grade local and systemic inflammation, and restored physical function. Our results demonstrate that lysosomal β-gal can be effectively leveraged to selectively eliminate senescent cells, providing a novel strategy to develop anti-aging interventions.

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A multidimensional systems biology analysis of cellular senescence in aging and disease

Background

Cellular senescence, a permanent state of replicative arrest in otherwise proliferating cells, is a hallmark of aging and has been linked to aging-related diseases. Many genes play a role in cellular senescence, yet a comprehensive understanding of its pathways is still lacking.

Results

We develop CellAge (http://genomics.senescence.info/cells), a manually curated database of 279 human genes driving cellular senescence, and perform various integrative analyses. Genes inducing cellular senescence tend to be overexpressed with age in human tissues and are significantly overrepresented in anti-longevity and tumor-suppressor genes, while genes inhibiting cellular senescence overlap with pro-longevity and oncogenes. Furthermore, cellular senescence genes are strongly conserved in mammals but not in invertebrates. We also build cellular senescence protein-protein interaction and co-expression networks. Clusters in the networks are enriched for cell cycle and immunological processes. Network topological parameters also reveal novel potential cellular senescence regulators. Using siRNAs, we observe that all 26 candidates tested induce at least one marker of senescence with 13 genes (*C9orf40*, *CDC25A*, *CDCA4*, *CKAP2*, *GTF3C4*, *HAUS4*, *IMMT*, *MCM7*, *MTHFD2*, *MYBL2*, *NEK2*, *NIPA2*, and *TCEB3*) decreasing cell number, activating p16/p21, and undergoing morphological changes that resemble cellular senescence.

Conclusions

Overall, our work provides a benchmark resource for researchers to study cellular senescence, and our systems biology analyses reveal new insights and gene regulators of cellular senescence.

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Systematic review and analysis of human proteomics aging studies unveils a novel proteomic aging clock and identifies key processes that change with age

The development of clinical interventions that significantly improve human healthspan requires robust markers of biological age as well as thoughtful therapeutic targets. To promote these goals, we performed a systematic review and analysis of human aging and proteomics studies. The systematic review includes 36 different proteomics analyses, each of which identified proteins that significantly changed with age. We discovered 1,128 proteins that had been reported by at least two or more analyses and 32 proteins that had been reported by five or more analyses. Each of these 32 proteins has known connections relevant to aging and age-related disease. GDF15, for example, extends both lifespan and healthspan when overexpressed in mice and is additionally required for the anti-diabetic drug metformin to exert beneficial effects on body weight and energy balance. Bioinformatic enrichment analyses of our 1,128 commonly identified proteins heavily implicated processes relevant to inflammation, the extracellular matrix, and gene regulation. We additionally propose a novel proteomic aging clock comprised of proteins that were reported to change with age in plasma in three or more different studies. Using a large patient cohort comprised of 3,301 subjects (aged 18–76 years), we demonstrate that this clock is able to accurately predict human age.

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ATM is a key driver of NF-κB-dependent DNA-damage-induced senescence, stem cell dysfunction and aging

NF-κB is a transcription factor activated in response to inflammatory, genotoxic and oxidative stress and important for driving senescence and aging. Ataxia-telangiectasia mutated (ATM) kinase, a core component of DNA damage response signaling, activates NF-κB in response to genotoxic and oxidative stress via post-translational modifications. Here we demonstrate that ATM is activated in senescent cells in culture and murine tissues from *Ercc1*-deficient mouse models of accelerated aging, as well as naturally aged mice. Genetic and pharmacologic inhibition of ATM reduced activation of NF-κB and markers of senescence and the senescence-associated secretory phenotype (SASP) in senescent $Ercc1^{-/-}$ MEFs. $Ercc1^{-/\Delta}$ mice heterozygous for *Atm* have reduced NF-κB activity and cellular senescence, improved function of muscle-derived stem/progenetor cells (MDSPCs) and extended healthspan with reduced age-related pathology especially age-related bone and intervertebral disc pathologies. In addition, treatment of $Ercc1^{-/\Delta}$ mice with the ATM inhibitor KU-55933 suppressed markers of senescence and SASP. Taken together, these results demonstrate that the ATM kinase is a major mediator of DNA damage-induced, NF-κB-mediated cellular senescence, stem cell dysfunction and aging and thus represents a therapeutic target to slow the progression of aging.

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Chronic Intermittent Hypoxia Triggers a Senescence-like Phenotype in Human White Preadipocytes

Obstructive sleep apnea (OSA) is a common sleep disorder associated with obesity. Emerging evidence suggest that OSA increases the risk of cardiovascular morbidity and mortality partly via accelerating the process of cellular aging. Thus, we sought to examine the effects of intermittent hypoxia (IH), a hallmark of OSA, on senescence in human white preadipocytes. We demonstrate that chronic IH is associated with an increased generation of mitochondrial reactive oxygen species along with increased prevalence of cells with nuclear localization of γH2AX & p16. A higher prevalence of cells positive for senescence-associated β-galactosidase activity was also evident with chronic IH exposure. Intervention with aspirin, atorvastatin or renin-angiotensin system (RAS) inhibitors effectively attenuated IH-mediated senescence-like phenotype. Importantly, the validity of *in vitro* findings was confirmed by examination of the subcutaneous abdominal adipose tissue which showed that OSA patients had a significantly higher percentage of cells with nuclear localization of γH2AX & p16 than non-OSA individuals (20.1 ± 10.8% vs. 10.3 ± 2.7%, $P_{adjusted} < 0.001$). Furthermore, the frequency of dual positive γH2AX & p16 nuclei in adipose tissue of OSA patients receiving statin, aspirin, and/or RAS inhibitors was comparable to non-OSA individuals. This study identifies chronic IH as a trigger of senescence-like phenotype in preadipocytes. Together, our data suggest that OSA may be considered as a senescence-related disorder.

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Heterochronic parabiosis regulates the extent of cellular senescence in multiple tissues

Matthew J. Yousefzadeh, John E. Wilkinson, Brian Hughes, Namrata Gadela, Warren C. Ladiges, Nam Vo, Laura J. Niedernhofer, Derek M. Huffman & Paul D. Robbins

GeroScience (2020) | Cite this article

151 Accesses | **7** Altmetric | Metrics

Abstract

An increase in the burden of senescent cells in tissues with age contributes to driving aging and the onset of age-related diseases. Genetic and pharmacologic elimination of senescent cells extends both health span and life span in mouse models. Heterochronic parabiosis in mice has been used to identify bloodborne, circulating pro- and anti-geronic factors able to drive or slow aging, respectively. However, whether factors in the circulation also regulate senescence is unknown. Here, we measured the expression of senescence and senescence-associated secretory phenotype (SASP) markers in multiple tissues from 4- to 18-month-old male mice that were either isochronically or heterochronically paired for 2 months. In heterochronic parabionts, the age-dependent increase in senescence and SASP marker expression was reduced in old mice exposed to a young environment, while senescence markers were concurrently increased in young heterochronic parabionts. These findings were supported by geropathology analysis using the Geropathology Grading Platform that showed a trend toward reduced hepatic lesions in old heterochronic parabionts. In summary, these results demonstrate that senescence is regulated in part by circulating geronic factors and suggest that one of the possible mediators of the rejuvenating effects with heterochronic parabiosis is through the reduction of the senescent cell burden.

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Using proteolysis-targeting chimera technology to reduce navitoclax platelet toxicity and improve its senolytic activity

Small molecules that selectively kill senescent cells (SCs), termed senolytics, have the potential to prevent and treat various age-related diseases and extend healthspan. The use of Bcl-xl inhibitors as senolytics is largely limited by their on-target and dose-limiting platelet toxicity. Here, we report the use of proteolysis-targeting chimera (PROTAC) technology to reduce the platelet toxicity of navitoclax (also known as ABT263), a Bcl-2 and Bcl-xl dual inhibitor, by converting it into PZ15227 (PZ), a Bcl-xl PROTAC, which targets Bcl-xl to the cereblon (CRBN) E3 ligase for degradation. Compared to ABT263, PZ is less toxic to platelets, but equally or slightly more potent against SCs because CRBN is poorly expressed in platelets. PZ effectively clears SCs and rejuvenates tissue stem and progenitor cells in naturally aged mice without causing severe thrombocytopenia. With further improvement, Bcl-xl PROTACs have the potential to become safer and more potent senolytic agents than Bcl-xl inhibitors.

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A BET family protein degrader provokes senolysis by targeting NHEJ and autophagy in senescent cells

Although cellular senescence acts primarily as a tumour suppression mechanism, the accumulation of senescent cells *in vivo* eventually exerts deleterious side effects through inflammatory/tumour-promoting factor secretion. Thus, the development of new drugs that cause the specific elimination of senescent cells, termed senolysis, is anticipated. Here, by an unbiased high-throughput screening of chemical compounds and a bio-functional analysis, we identify BET family protein degrader (BETd) as a promising senolytic drug. BETd provokes senolysis through two independent but integrated pathways; the attenuation of non-homologous end joining (NHEJ), and the up-regulation of autophagic gene expression. BETd treatment eliminates senescent hepatic stellate cells in obese mouse livers, accompanied by the reduction of liver cancer development. Furthermore, the elimination of chemotherapy-induced senescent cells by BETd increases the efficacy of chemotherapy against xenograft tumours in immunocompromised mice. These results reveal the vulnerability of senescent cells and open up possibilities for its control.

The mTOR pathway is necessary for survival of mice with short telomeres

Iole Ferrara-Romeo, Paula Martinez, Sarita Saraswati, Kurt Whittemore, Osvaldo Graña-Castro, Lydia Thelma Poluha, Rosa Serrano, Elena Hernandez-Encinas, Carmen Blanco-Aparicio, Juana Maria Flores & Maria A. Blasco

Nature Communications **11**, Article number: 1168 (2020) | Cite this article

3087 Accesses | **83** Altmetric | Metrics

Abstract

Telomerase deficiency leads to age-related diseases and shorter lifespans. Inhibition of the mechanistic target of rapamycin (mTOR) delays aging and age-related pathologies. Here, we show that telomerase deficient mice with short telomeres (G2-*Terc*$^{-/-}$) have an hyper-activated mTOR pathway with increased levels of phosphorylated ribosomal S6 protein in liver, skeletal muscle and heart, a target of mTORC1. Transcriptional profiling confirms mTOR activation in G2-*Terc*$^{-/-}$ livers. Treatment of G2-*Terc*$^{-/-}$ mice with rapamycin, an inhibitor of mTORC1, decreases survival, in contrast to lifespan extension in wild-type controls. Deletion of mTORC1 downstream S6 kinase 1 in G3-*Terc*$^{-/-}$ mice also decreases longevity, in contrast to lifespan extension in single S6K1$^{-/-}$ female mice. These findings demonstrate that mTOR is important for survival in the context of short telomeres, and that its inhibition is deleterious in this setting. These results are of clinical interest in the case of human syndromes characterized by critically short telomeres.

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Rapamycin rejuvenates oral health in aging mice

Periodontal disease is an age-associated disorder clinically defined by periodontal bone loss, inflammation of the specialized tissues that surround and support the tooth, and microbiome dysbiosis. Currently, there is no therapy for reversing periodontal disease, and treatment is generally restricted to preventive measures or tooth extraction. The FDA-approved drug rapamycin slows aging and extends lifespan in multiple organisms, including mice. Here we demonstrate that short-term treatment with rapamycin rejuvenates the aged oral cavity of elderly mice, including regeneration of periodontal bone, attenuation of gingival and periodontal bone inflammation, and revertive shift of the oral microbiome toward a more youthful composition. This provides a geroscience strategy to potentially rejuvenate oral health and reverse periodontal disease in the elderly.

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Rosuvastatin Prevents the Exacerbation of Atherosclerosis in Ligature-Induced Periodontal Disease Mouse Model

Periodontitis is a local and systemic inflammatory condition and a risk factor of atherosclerosis, but no studies investigated the effect of a statin on atherogenesis affected by severe periodontitis. In this study, we investigated the effect of rosuvastatin (RSV) on atherogenesis in Apolipoprotein E-deficient mice receiving silk ligature placement around the maxillary second molars. Mice with the ligature placement developed severe periodontitis and vascular inflammation. RSV significantly inhibited the development of periodontitis and vascular inflammation and remarkably blocked the increased lipid deposition and the atherogenic gene expression in the arterial wall and aortic sinus induced by severe periodontitis. To understand the mechanistic effect of RSV on periodontitis-associated atherogenesis, we investigated the *in vitro* effect of RSV on various effect of TNF-α, a major proinflammatory cytokine for periodontitis and atherogenesis. We found that RSV notably inhibited the TNF-α-induced osteoclast formation, endothelial cell phenotypic changes, foam cell formation, and the expression of CD47 and other oncogenes in arterial smooth muscle cells. Taken together, our study indicates that RSV prevents the exacerbation of atherosclerosis induced periodontitis by inhibiting local, systemic and vascular inflammation, as well as the expression of CD47 from arterial smooth muscle cells in mice.

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Bayesian neural networks for the optimisation of biological clocks in humans

G Alfonso, Juan R Gonzalez

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Abstract

DNA methylation is related to aging. Some researchers, such as Horvath or Levine have managed to create epigenetic and biological clocks that predict chronological age using methylation data. These authors used Elastic Net methodology to build age predictors that had a high prediction accuracy. In this article, we propose to improve their performance by incorporating an additional step using neural networks trained with Bayesian learning. We shown that this approach outperforms the results obtained when using Horvath's method, neural networks directly, or when using other training algorithms, such as Levenberg-Marquardt's algorithm. The R-squared value obtained when using our proposed approach in empirical (out-of sample) data was 0.934, compared to 0.914 when using a different training algorithm (Levenberg Marquard), or 0.910 when applying the neural network directly (e.g. without first reducing the dimensionality of the data). The results were also tested in independent datasets that were not used during the training phase. Our method obtained better R-squared values and RMSE than Horvath's and Levine's method in 8 independent datasets. We demonstrate that building an age predictor using a Bayesian based algorithm provides accurate age predictions. This method is implemented in an R function, which is available through a package created for predicting purposes and is applicable to methylation data. This will help to elucidate the role of DNA methylation age in complex diseases or traits related to aging.

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Association of 4 epigenetic clocks with measures of functional health, cognition, and all-cause mortality in The Irish Longitudinal Study on Ageing (TILDA)

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Abstract

The aging process is characterized by the presence of high interindividual variation between individuals of the same chronical age prompting a search for biomarkers that capture this heterogeneity. The present study examines the associations of four epigenetic clocks - Horvath, Hannum, PhenoAge, GrimAge - with a wide range of clinical phenotypes, and with all-cause mortality at up to 10-year follow-up in a sample of 490 participants in the Irish Longitudinal Study on Ageing (TILDA). Results indicate that the GrimAge clock represents a step-improvement in the predictive utility of the epigenetic clocks for identifying age-related decline in an array of clinical phenotypes.

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Systematic age-, organ-, and diet-associated ionome remodeling and the development of ionomic aging clocks

Bohan Zhang, Dmitriy I. Podolskiy, Marco Mariotti, Javier Seravalli, Vadim N. Gladyshev

Aging involves coordinated yet distinct changes in organs and systems throughout life, including changes in essential trace elements. However, how aging affects tissue element composition (ionome) and how these changes lead to dysfunction and disease remain unclear. Here, we quantified changes in the ionome across eight organs and 16 age groups of mice. This global profiling revealed novel interactions between elements at the level of tissue, age, and diet, and allowed us to achieve a broader, organismal view of the aging process. We found that while the entire ionome steadily transitions along the young-to-old trajectory, individual organs are characterized by distinct element changes. The ionome of mice on calorie restriction (CR) moved along a similar but shifted trajectory, pointing that at the organismal level this dietary regimen changes metabolism in order to slow down aging. However, in some tissues CR mimicked a younger state of control mice. Even though some elements changed with age differently in different tissues, in general aging was characterized by the reduced levels of elements as well as their increased variance. The dataset we prepared also allowed to develop organ-specific, ionome-based markers of aging that could help monitor the rate of aging. In some tissues, these markers reported the lifespan-extending effect of CR. These aging biomarkers have the potential to become an accessible tool to test the age-modulating effects of interventions.

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Interspecies differences in proteome turnover kinetics are correlated with lifespans and energetic demands

Kyle Swovick, Denis Firsanov, Kevin A. Welle, Jennifer R. Hryhorenko, John P. Wise, Craig George, Todd L. Sformo, Andrei Seluanov, Vera Gorbunova, Sina Ghaemmaghami

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Abstract

Cells continually degrade and replace damaged and old proteins. However, the high energetic demand of protein turnover generates reactive oxygen species (ROS) that compromise the long-term health of the proteome. Thus, the relationship between aging, protein turnover and energetic demand remains unclear. Here, we used a proteomic approach to measure rates of protein turnover within primary fibroblasts isolated from a number of species with diverse lifespans including the longest-lives rodent, the naked mole rat and the longest-lived mammal, the bowhead whale. We show that organismal lifespan is negatively correlated with turnover rates of highly abundant proteins. In comparison to mice, cells from long-lived naked mole rats have slower rates of protein turnover, lower levels of ATP production and reduced ROS levels. Despite having slower rates of protein turnover, naked mole rat cells tolerate protein misfolding stress more effectively than mouse cells. We suggest that in lieu of rapid constitutive turnover, long-lived species may have evolved more energetically efficient mechanisms for selective detection and clearance of damaged proteins.

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Sample multiplexing for targeted pathway proteomics in aging mice

Pathway proteomics strategies measure protein expression changes in specific cellular processes that carry out related functions. Using targeted tandem mass tags-based sample multiplexing, hundreds of proteins can be quantified across 10 or more samples simultaneously. To facilitate these highly complex experiments, we introduce a strategy that provides complete control over targeted sample multiplexing experiments, termed Tomahto, and present its implementation on the Orbitrap Tribrid mass spectrometer platform. Importantly, this software monitors via the external desktop computer to the data stream and inserts optimized MS2 and MS3 scans in real time based on an application programming interface with the mass spectrometer. Hundreds of proteins of interest from diverse biological samples can be targeted and accurately quantified in a sensitive and high-throughput fashion. It achieves sensitivity comparable to, if not better than, deep fractionation and requires minimal total sample input (~10 µg). As a proof-of-principle experiment, we selected four pathways important in metabolism- and inflammation-related processes (260 proteins/520 peptides) and measured their abundance across 90 samples (nine tissues from five old and five young mice) to explore effects of aging. Tissue-specific aging is presented here and we highlight the role of inflammation- and metabolism-related processes in white adipose tissue. We validated our approach through comparison with a global proteome survey across the tissues, work that we also provide as a general resource for the community.

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Moderation of mitochondrial respiration mitigates metabolic syndrome of aging

Deregulation of mitochondrial dynamics leads to the accumulation of oxidative stress and unhealthy mitochondria; consequently, this accumulation contributes to premature aging and alterations in mitochondria linked to metabolic complications. We postulate that restrained mitochondrial ATP synthesis might alleviate age-associated disorders and extend healthspan in mammals. Herein, we prepared a previously discovered mitochondrial complex IV moderate inhibitor in drinking water and orally administered to standard-diet-fed, wild-type C57BL/6J mice every day for up to 16 mo. No manifestation of any apparent toxicity or deleterious effect on studied mouse models was observed. The impacts of an added inhibitor on a variety of mitochondrial functions were analyzed, such as respiratory activity, mitochondrial bioenergetics, and biogenesis, and a few age-associated comorbidities, including reactive oxygen species (ROS) production, glucose abnormalities, and obesity in mice. It was found that mitochondrial quality, dynamics, and oxidative metabolism were greatly improved, resulting in lean mice with a specific reduction in visceral fat plus superb energy and glucose homeostasis during their aging period compared to the control group. These results strongly suggest that a mild interference in ATP synthesis through moderation of mitochondrial activity could effectively up-regulate mitogenesis, reduce ROS production, and preserve mitochondrial integrity, thereby impeding the onset of metabolic syndrome. We conclude that this inhibitory intervention in mitochondrial respiration rectified the age-related physiological breakdown in mice by protecting mitochondrial function and markedly mitigated certain undesired primary outcomes of metabolic syndrome, such as obesity and type 2 diabetes. This intervention warrants further research on the treatment of metabolic syndrome of aging in humans.

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SynergyAge: a curated database for synergistic and antagonistic interactions of longevity-associated genes

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This article is a preprint and has not been certified by peer review [what does this mean?].

Abstract | Full Text | Info/History | Metrics | Preview PDF

ABSTRACT

Interventional studies on genetic modulators of longevity have significantly changed gerontology. While available lifespan data is continually accumulating, further understanding of the aging process is still limited by the poor understanding of epistasis and of the non-linear interactions between multiple longevity-associated genes. Unfortunately, based on observations so far, there is no simple method to predict the cumulative impact of genes on lifespan. As a step towards applying predictive methods, but also to provide information for a guided design of epistasis lifespan experiments, we developed SynergyAge - a database containing genetic and lifespan data for animal models obtained through multiple longevity-modulating interventions. The studies included in SynergyAge focus on the lifespan of animal strains which are modified by at least two genetic interventions, with single gene mutants included as reference. SynergyAge, which is publicly available at www.synergyage.info, provides an easy to use web-platform for browsing, searching and filtering through the data, as well as a network-based interactive module for visualization and analysis.

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Deficiency of CD44 prevents thoracic aortic dissection in a murine model

Thoracic aortic dissection (TAD) is a life-threatening vascular disease. We showed that CD44, a widely distributed cell surface adhesion molecule, has an important role in inflammation. In this study, we examined the role of CD44 in the development of TAD. TAD was induced by the continuous infusion of β-aminopropionitrile (BAPN), a lysyl oxidase inhibitor, and angiotensin II (AngII) for 7 days in wild type (WT) mice and CD44 deficient ($CD44^{-/-}$) mice. The incidence of TAD in $CD44^{-/-}$ mice was significantly reduced compared with WT mice (44% and 6%, $p < 0.01$). Next, to evaluate the initial changes, aortic tissues at 24 hours after BAPN/AngII infusion were examined. Neutrophil accumulation into thoracic aortic adventitia in $CD44^{-/-}$ mice was significantly decreased compared with that in WT mice ($5.7 \pm 0.3\%$ and $1.6 \pm 0.4\%$, $p < 0.01$). In addition, BAPN/AngII induced interleukin-6, interleukin-1β, matrix metalloproteinase-2 and matrix metalloproteinase-9 in WT mice, all of which were significantly reduced in $CD44^{-/-}$ mice (all $p < 0.01$). *In vitro* transmigration of neutrophils from $CD44^{-/-}$ mice through an endothelial monolayer was significantly decreased by 18% compared with WT mice ($p < 0.01$). Our findings indicate that CD44 has a critical role in TAD development in association with neutrophil infiltration into adventitia.

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Discovery of novel biomarkers for atherosclerotic aortic aneurysm through proteomics-based assessment of disease progression

Since aortic aneurysms (AAs) are mostly asymptomatic, but they have a high mortality rate upon rupture, their detection and progression evaluation are clinically important issues. To discover diagnostic biomarkers for AA, we performed proteome analysis of aortic media from patients with thoracic atherosclerotic AA (TAAA), comparing protein levels between the aneurysm and normal tissue areas. After hierarchical clustering analysis of the proteome analysis data, tissue samples were classified into three groups, regardless of morphological features. This classification was shown to reflect disease progression stage identified by pathological examination. This proteomics-based staging system enabled us to identify more significantly altered proteins than the morphological classification system. In subsequent data analysis, Niemann-Pick disease type C2 protein (NPC2) and insulin-like growth factor-binding protein 7 (IGFBP7) were selected as novel biomarker candidates for AA and were compared with the previously reported biomarker, thrombospondin 1 (THBS1). Blood concentrations of NPC2 and IGFBP7 were significantly increased, while THBS1 levels were decreased in TAAA and abdominal atherosclerotic AA patients. Receiver operating characteristic analysis of AA patients and healthy controls showed that NPC2 and IGFBP7 have higher specificity and sensitivity than THBS1. Thus, NPC2 and IGFBP7 are promising biomarkers for the detection and progression evaluation of AA.

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Supraphysiological protection from replication stress does not extend mammalian lifespan

Replication Stress (RS) is a type of DNA damage generated at the replication fork, characterized by single-stranded DNA (ssDNA) accumulation, and which can be caused by a variety of factors. Previous studies have reported elevated RS levels in aged cells. In addition, mouse models with a deficient RS response show accelerated aging. However, the relevance of endogenous or physiological RS, compared to other sources of genomic instability, for the normal onset of aging is unknown. We have performed long term survival studies of transgenic mice with extra copies of the *Chk1* and/or *Rrm2* genes, which we previously showed extend the lifespan of a progeroid ATR-hypomorphic model suffering from high levels of RS. In contrast to their effect in the context of progeria, the lifespan of *Chk1, Rrm2* and *Chk1/Rrm2* transgenic mice was similar to WT littermates in physiological settings. Most mice studied died due to tumors -mainly lymphomas- irrespective of their genetic background. Interestingly, a higher but not statistically significant percentage of transgenic mice developed tumors compared to WT mice. Our results indicate that supraphysiological protection from RS does not extend lifespan, indicating that RS may not be a relevant source of genomic instability on the onset of normal aging.

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The Y chromosome may contribute to sex-specific ageing in *Drosophila*

Emily J. Brown, Alison H. Nguyen & Doris Bachtrog

Nature Ecology & Evolution (2020) | Cite this article

Abstract

Heterochromatin suppresses repetitive DNA, and a loss of heterochromatin has been observed in aged cells of several species, including humans and *Drosophila*. Males often contain substantially more heterochromatic DNA than females, due to the presence of a large, repeat-rich Y chromosome, and male flies generally have a shorter average lifespan than females. Here we show that repetitive DNA becomes de-repressed more rapidly in old male flies relative to females, and repeats on the Y chromosome are disproportionally mis-expressed during ageing. This is associated with a loss of heterochromatin at repetitive elements during ageing in male flies, and a general loss of repressive chromatin in aged males away from pericentromeric regions and the Y. By generating flies with different sex chromosome karyotypes (XXY females and X0 and XYY males), we show that repeat de-repression and average lifespan is correlated with the number of Y chromosomes. This suggests that sex-specific chromatin differences may contribute to sex-specific ageing in flies.

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Long-term treatment with spermidine increases health span of middle-aged Sprague-Dawley male rats.

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Author information

Abstract

Let alone calorie restriction, life span extension in higher organisms has proven to be difficult to achieve using simple drugs. Previous studies have shown that the polyamine spermidine increased the maximum life span in C. elegans and the median life span in mice. However, younger subjects (< 40 years of age) are infrequently prescribed nor self-medicating with antiaging drugs. Therefore, in the present study, we aimed at assessing the effect of long-term treatment with spermidine given in the drinking water on behavioral performance and longevity of male, middle-aged Sprague-Dawley rats. We report that spermidine given in the drinking water did not extend neither the median nor the maximum life span of the middle-aged male Sprague-Dawley rats. However, spermidine treatment had a beneficial effect on the body weight and the kidney tubules, liver, and heart morphology. Behaviorally, spermidine led to a reduction in anxiety and an increase in curiosity, as assessed by exploratory behavior. Moreover, long-term treatment with spermidine enhanced autophagy in the brain and led to a diminished expression of the inflammatory markers, Tgfb, CD11b, Fcgr1, Stat1, CR3, and GFAP mRNAs in several cortical region and hippocampus of the treated rats suggesting that one beneficial effect of the long-term treatment with spermidine is an attenuated proinflammatory state in the aged brain. Our results suggest that long-term treatment with spermidine increases health span of middle-aged rats by attenuating neuroinflammation and improving anxiety and exploratory behavior.

NoxO1 Knockout Promotes Longevity in Mice

by Tim Schader, Christina Reschke, Manuela Spaeth, Susanne Wienstroer, Szeka Wong and Katrin Schröder *

According to the free radical theory of aging, reactive oxygen species (ROS) have been proposed to be a major cause of aging for a long time. Meanwhile, it became clear that ROS have diverse functions in a healthy organism. They act as second messengers, and as transient inhibitors of phosphatases and others. In fact, their detrimental role is highly dependent on the context of their production. NADPH oxidases (Nox) have been discovered as a controllable source of ROS. NoxO1 enables constitutive ROS formation by Nox1 by acting as a constitutively active cytosolic subunit of the complex. We previously found that both Nox1 and NoxO1 were highly expressed in the colon, and that NoxO1-/- deficiency reduces colon health. We hypothesized that a healthy colon potentially contributes to longevity and NoxO1 deficiency would reduce lifetime, at least in mouse. In contrast, here we provide evidence that the knockout of NoxO1 results in an elongated life expectancy of mice. No better endothelial function, nor an improved expression of genes related to longevity, such as Sirt1, were found, and therefore may not serve as an explanation for a longer life in NoxO1 deficiency. Rather minor systemic differences, such as lower body weight occur. As a potential reason for longer life, we suggest better DNA repair capacity in NoxO1 deficient mice. Although final fatal DNA damage appears similar between wildtype and NoxO1 knockout animals, we identified less intermediate DNA damage in colon cells of NoxO1-/- mice, while the number of cells with intact DNA is elevated in NoxO1-/- colons. We conclude that NoxO1 deficiency prolongs lifetime of mice, which correlates with less intermediate and potentially fixable DNA damage at least in colon cells. View Full-Text

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Isotopic Nitrogen-15 Labeling of Mice Identified Long-lived Proteins of the Renal Basement Membranes

The kidney is comprised of highly complex structures that rely on self-maintenance for their functions, and tissue repair and regeneration in renal diseases. We devised a proteomics assay to measure the turnover of individual proteins in mouse kidney. Mice were metabolically labeled with a specially formulated chow containing nitrogen-15 (^{15}N) with the absence of normal ^{14}N atoms. Newly synthesized proteins with ^{15}N contents were distinguished from their ^{14}N counterparts by mass spectrometry. In total, we identified over 4,000 proteins from the renal cortex with a majority of them contained only ^{15}N. About 100 proteins had both ^{14}N- and ^{15}N-contents. Notably, the long-lived proteins that had large $^{14}N/^{15}N$ ratios were mostly matrix proteins. These included proteins such as type IV and type VI collagen, laminin, nidogen and perlecan/HSPG2 that constitute the axial core of the glomerular basement membrane (GBM). In contrast, the surface lamina rara proteins such as agrin and integrin had much shorter longevity, suggesting their faster regeneration cycle. The data illustrated matrix proteins that constitute the basement membranes in the renal cortex are constantly renewed in an ordered fashion. In perspective, the global profile of protein turnover is usefully in understanding the protein-basis of GBM maintenance and repair.

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Leukocyte Telomere Length Is Unrelated to Cognitive Performance Among Non-Demented and Demented Persons: An Examination of Long Life Family Study Participants

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Abstract

Objective:

Leukocyte telomere length (LTL) is a widely hypothesized biomarker of biological aging. Persons with shorter LTL may have a greater likelihood of developing dementia. We investigate whether LTL is associated with cognitive function, differently for individuals without cognitive impairment *versus* individuals with dementia or incipient dementia.

Method:

Enrolled subjects belong to the Long Life Family Study (LLFS), a multi-generational cohort study, where enrollment was predicated upon exceptional family longevity. Included subjects had valid cognitive and telomere data at baseline. Exclusion criteria were age ≤ 60 years, outlying LTL, and missing sociodemographic/clinical information. Analyses were performed using linear regression with generalized estimating equations, adjusting for sex, age, education, country, generation, and lymphocyte percentage.

Results:

Older age and male gender were associated with shorter LTL, and LTL was significantly longer in family members than spouse controls ($p < 0.005$). LTL was not associated with working or episodic memory, semantic processing, and information processing speed for 1613 cognitively unimpaired individuals as well as 597 individuals with dementia or incipient dementia ($p < 0.005$), who scored significantly lower on all cognitive domains ($p < 0.005$).

Conclusions:

Within this unique LLFS cohort, a group of families assembled on the basis of exceptional survival, LTL is unrelated to cognitive ability for individuals with and without cognitive impairment. LTL does not change in the context of degenerative disease for these individuals who are biologically younger than the general population.

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Large-scale proteomic analysis of Alzheimer's disease brain and cerebrospinal fluid reveals early changes in energy metabolism associated with microglia and astrocyte activation

Our understanding of Alzheimer's disease (AD) pathophysiology remains incomplete. Here we used quantitative mass spectrometry and coexpression network analysis to conduct the largest proteomic study thus far on AD. A protein network module linked to sugar metabolism emerged as one of the modules most significantly associated with AD pathology and cognitive impairment. This module was enriched in AD genetic risk factors and in microglia and astrocyte protein markers associated with an anti-inflammatory state, suggesting that the biological functions it represents serve a protective role in AD. Proteins from this module were elevated in cerebrospinal fluid in early stages of the disease. In this study of >2,000 brains and nearly 400 cerebrospinal fluid samples by quantitative proteomics, we identify proteins and biological processes in AD brains that may serve as therapeutic targets and fluid biomarkers for the disease.

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Longitudinal Quantification of Metabolites and Macromolecules Reveals Age- and Sex-Related Changes in the Healthy Fischer 344 Rat Brain

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Abstract

Normal aging is associated with numerous biological changes including altered brain metabolism and tissue chemistry. In vivo characterization of the neurochemical profile during aging is possible using magnetic resonance spectroscopy, a powerful non-invasive technique capable of quantifying brain metabolites involved in physiological processes that become impaired with age. A prominent macromolecular signal underlies those of brain metabolites and is particularly visible at high fields; parameterization of this signal into components improves quantification and expands the number of biomarkers comprising the neurochemical profile. The present study reports, for the first time, the simultaneous absolute quantification of brain metabolites and individual macromolecules in aging male and female Fischer 344 rats, measured longitudinally using proton magnetic resonance spectroscopy at 7T. We identified age- and sex-related changes in neurochemistry, with prominent differences in metabolites implicated in anaerobic energy metabolism, antioxidant capacity, and neuroprotection, as well as numerous macromolecule changes. These findings contribute to our understanding of the neurobiological processes associated with healthy aging, critical for the proper identification and management of pathological aging trajectories.

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Biological sex and DNA repair deficiency drive Alzheimer's disease via systemic metabolic remodeling and brain mitochondrial dysfunction

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Abstract

Alzheimer's disease (AD) is an incurable neurodegenerative disease that is more prevalent in women. The increased risk of AD in women is not well understood. It is well established that there are sex differences in metabolism and that metabolic alterations are an early component of AD. We utilized a cross-species approach to evaluate conserved metabolic alterations in the serum and brain of human AD subjects, two AD mouse models, a human cell line, and two *Caenorhabditis elegans* AD strains. We found a mitochondrial complex I-specific impairment in cortical synaptic brain mitochondria in female, but not male, AD mice. In the hippocampus, Polβ haploinsufficiency caused synaptic complex I impairment in male and female mice, demonstrating the critical role of DNA repair in mitochondrial function. In non-synaptic, glial-enriched, mitochondria from the cortex and hippocampus, complex II-dependent respiration increased in female, but not male, AD mice. These results suggested a glial upregulation of fatty acid metabolism to compensate for neuronal glucose hypometabolism in AD. Using an unbiased metabolomics approach, we consistently observed evidence of systemic and brain metabolic remodeling with a shift from glucose to lipid metabolism in humans with AD, and in AD mice. We determined that this metabolic shift is necessary for cellular and organismal survival in *C. elegans*, and human cell culture AD models. We observed sex-specific, systemic, and brain metabolic alterations in humans with AD, and that these metabolite changes significantly correlate with amyloid and tau pathology. Among the most significant metabolite changes was the accumulation of glucose-6-phosphate in AD, an inhibitor of hexokinase and rate-limiting metabolite for the pentose phosphate pathway (PPP). Overall, we identified novel mechanisms of glycolysis inhibition, PPP, and tricarboxylic acid cycle impairment, and a neuroprotective augmentation of lipid metabolism in AD. These findings support a sex-targeted metabolism-modifying strategy to prevent and treat AD.

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Age-Related Changes in Chimpanzee (*Pan troglodytes*) Cognition: Cross-Sectional and Longitudinal Analyses

William D Hopkins, Mary Catherine Mareno, Sarah J Neal Webb, Steven J Schapiro, Mary Ann Raghanti, Chet C Sherwood

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Abstract

Chimpanzees are the species most closely related to humans yet age-related changes in brain and cognition remain poorly understood. The lack of studies on age-related changes in cognition in chimpanzees is particularly unfortunate in light of the recent evidence demonstrating that this species naturally develops Alzheimer's disease (AD) neuropathology. Here, we tested 213 young, middle-aged, and elderly chimpanzees on the Primate Cognitive Test Battery (PCTB), a set of 13 tasks that assess physical and social cognition in nonhuman primates. A subset of these chimpanzees (n=146) were tested a second time on a portion of the PCTB tasks as a means of evaluating longitudinal changes in cognition. Cross-sectional analyses revealed a significant quadratic association between age and cognition with younger and older chimpanzees performing more poorly than middle-aged individuals. Longitudinal analyses showed that, while young chimpanzees' performance improved from test 1 to test 2, middle-aged and elderly chimpanzees' performance showed significant decline over time. The collective data show that chimpanzees, like other nonhuman primates, show age-related decline in cognition. Further investigations into whether the observed cognitive decline is associated with AD pathologies in chimpanzees would be invaluable in understanding the comparative biology of aging and neuropathology in primates.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Small molecule cognitive enhancer reverses age-related memory decline in mice

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ABSTRACT

With increased life expectancy, age-associated cognitive decline becomes a growing concern. The integrated stress response (ISR) is activated during aging and contributes to age-related brain phenotypes. We demonstrate that treatment with the drug-like small-molecule ISR inhibitor ISRIB reverses ISR activation in the brain, as indicated by decreased activating transcription factor 4 (ATF4) protein levels. Furthermore, ISRIB treatment reverses spatial memory deficits and ameliorates working memory in old mice. At the cellular level in the hippocampus, ISR inhibition i) rescues intrinsic neuronal electrophysiological properties, ii) restores spine density and iii) reduces immune profiles, specifically interferon and T cell-mediated responses. Thus, pharmacological interference with the ISR emerges as a promising intervention strategy for combating age-related cognitive decline.

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Exercise rejuvenates quiescent skeletal muscle stem cells in old mice through restoration of Cyclin D1

Ageing impairs tissue repair. This defect is pronounced in skeletal muscle, whose regeneration by muscle stem cells (MuSCs) is robust in young-adult animals, but inefficient in older organisms. Despite this functional decline, old MuSCs are amenable to rejuvenation through strategies that improve the systemic milieu, such as heterochronic parabiosis. One such strategy, exercise, has long been appreciated for its benefits on healthspan, but its effects on aged stem-cell function in the context of tissue regeneration are incompletely understood. Here, we show that exercise in the form of voluntary wheel running accelerates muscle repair in old mice and improves old MuSC function. Through transcriptional profiling and genetic studies, we discovered that the restoration of old MuSC activation ability hinges on restoration of Cyclin D1, whose expression declines with age in MuSCs. Pharmacologic studies revealed that Cyclin D1 maintains MuSC activation capacity by repressing TGF-β signalling. Taken together, these studies demonstrate that voluntary exercise is a practicable intervention for old MuSC rejuvenation. Furthermore, this work highlights the distinct role of Cyclin D1 in stem-cell quiescence.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Germline burden of rare damaging variants negatively affects human healthspan and lifespan

Anastasia V Shindyapina, Aleksandr A Zenin, Andrei E Tarkhov, Didac Santesmasses, Peter O Fedichev, Vadim N Gladyshev

Heritability of human lifespan is 23-33% as evident from twin studies. Genome-wide association studies explored this question by linking particular alleles to lifespan traits. However, genetic variants identified so far can explain only a small fraction of lifespan heritability in humans. Here, we report that the burden of rarest protein-truncating variants (PTVs) in two large cohorts is negatively associated with human healthspan and lifespan, accounting for 0.4 and 1.3 years of their variability, respectively. In addition, longer-living individuals possess both fewer rarest PTVs and less damaging PTVs. We further find that somatic accumulation of PTVs accounts for only a small fraction of mortality and morbidity acceleration and hence is unlikely to be causal in aging. We conclude that rare damaging mutations, both inherited and accumulated throughout life, contribute to the aging process, and that burden of ultra-rare variants in combination with common alleles better explain apparent heritability of human lifespan.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Trans-biobank analysis with 676,000 individuals elucidates the association of polygenic risk scores of complex traits with human lifespan

While polygenic risk scores (PRSs) are poised to be translated into clinical practice through prediction of inborn health risks[1], a strategy to utilize genetics to prioritize modifiable risk factors driving heath outcome is warranted[2]. To this end, we investigated the association of the genetic susceptibility to complex traits with human lifespan in collaboration with three worldwide biobanks (n_{total} = 675,898; BioBank Japan (n = 179,066), UK Biobank (n = 361,194) and FinnGen (n = 135,638)). In contrast to observational studies, in which discerning the cause-and-effect can be difficult, PRSs could help to identify the driver biomarkers affecting human lifespan. A high systolic blood pressure PRS was trans-ethnically associated with a shorter lifespan (hazard ratio = 1.03[1.02–1.04], $P_{meta} = 3.9 \times 10^{-13}$) and parental lifespan (hazard ratio = 1.06[1.06–1.07], $P = 2.0 \times 10^{-86}$). The obesity PRS showed distinct effects on lifespan in Japanese and European individuals ($P_{heterogeneity} = 9.5 \times 10^{-8}$ for BMI). The causal effect of blood pressure and obesity on lifespan was further supported by Mendelian randomization studies. Beyond genotype–phenotype associations, our trans-biobank study offers a new value of PRSs in prioritization of risk factors that could be potential targets of medical treatment to improve population health.

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Circadian regulation of mitochondrial uncoupling and lifespan

Because old age is associated with defects in circadian rhythm, loss of circadian regulation is thought to be pathogenic and contribute to mortality. We show instead that loss of specific circadian clock components Period (Per) and Timeless (Tim) in male *Drosophila* significantly extends lifespan. This lifespan extension is not mediated by canonical diet-restriction longevity pathways but is due to altered cellular respiration via increased mitochondrial uncoupling. Lifespan extension of per mutants depends on mitochondrial uncoupling in the intestine. Moreover, upregulated uncoupling protein UCP4C in intestinal stem cells and enteroblasts is sufficient to extend lifespan and preserve proliferative homeostasis in the gut with age. Consistent with inducing a metabolic state that prevents overproliferation, mitochondrial uncoupling drugs also extend lifespan and inhibit intestinal stem cell overproliferation due to aging or even tumorigenesis. These results demonstrate that circadian-regulated intestinal mitochondrial uncoupling controls longevity in *Drosophila* and suggest a new potential anti-aging therapeutic target.

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Genomics. 2020 Apr 19. pii: S0888-7543(19)30695-0. doi: 10.1016/j.ygeno.2020.04.010. [Epub ahead of print]

Finding of novel telomeric repeats and their distribution in the human genome.

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⊕ Author information

Abstract

Telomeres, the nucleoprotein structures, located at the end of the chromosomes are correlated with cancer and aging. The accelerated telomere attrition can accelerate human aging and leads to the progression of several cancers. Our work describes the finding of two novel telomeric repeats "CACAGA" and "TCTCTGCGCCTGCGCCGGCGCGGCGCGCC" and demonstrates their distribution in human chromosomes compare to the reported telomeric repeat TTAGGG. Simultaneously, the distance between the adjacent telomeric repeats (loop) was determined and the presence of shorter loops in the telomeric regions might address the correlation between the telomere attrition and senescence condition in human.

Aging (Albany NY). 2020 May 1;12. doi: 10.18632/aging.103093. [Epub ahead of print]

Age-related shifts in gut microbiota contribute to cognitive decline in aged rats.

Li Y[1,2], Ning L[1], Yin Y[1], Wang R[2], Zhang Z[1], Hao L[1], Wang B[3], Zhao X[1], Yang X[1], Yin L[1], Wu S[1], Guo D[1], Zhang C[1].

Author information

Abstract

Cognitive function declines during the aging process, meanwhile, gut microbiota of the elderly changed significantly. Although previous studies have reported the effect of gut microbiota on learning and memory, all the reports were based on various artificial interventions to change the gut microbiota without involvement of aging biological characteristics. Here, we investigated the effect of aged gut microbiota on cognitive function by using fecal microbiota transplantation (FMT) from aged to young rats. Results showed that FMT impaired cognitive behavior in young recipient rats; decreased the regional homogeneity in medial prefrontal cortex and hippocampus; changed synaptic structures and decreased dendritic spines; reduced expression of brain-derived neurotrophic factor (BDNF), N-methyl-D-aspartate receptor NR1 subunit, and synaptophysin; increased expression of advanced glycation end products (AGEs) and receptor for AGEs (RAGE). All these behavioral, brain structural and functional alterations induced by FMT reflected cognitive decline. In addition, FMT increased levels of pro-inflammatory cytokines and oxidative stress in young rats, indicating that inflammation and oxidative stress may underlie gut-related cognitive decline in aging. This study provides direct evidence for the contribution of gut microbiota to the cognitive decline during normal aging and suggests that restoring microbiota homeostasis in the elderly may improve cognitive function.

C. elegans aging research

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Aging Cell. 2020 Apr 16:e13141. doi: 10.1111/acel.13141. [Epub ahead of print]

Shorter life and reduced fecundity can increase colony fitness in virtual Caenorhabditis elegans.

Galimov ER[1], Gems D[1].

⊕ Author information

Abstract

In the nematode Caenorhabditis elegans, loss of function of many genes leads to increases in lifespan, sometimes of a very large magnitude. Could this reflect the occurrence of programmed death that, like apoptosis of cells, promotes fitness? The notion that programmed death evolves as a mechanism to remove worn out, old individuals in order to increase food availability for kin is not supported by classic evolutionary theory for most species. However, it may apply in organisms with colonies of closely related individuals such as C. elegans in which largely clonal populations subsist on spatially limited food patches. Here, we ask whether food competition between nonreproductive adults and their clonal progeny could favor programmed death by using an in silico model of C. elegans. Colony fitness was estimated as yield of dauer larva propagules from a limited food patch. Simulations showed that not only shorter lifespan but also shorter reproductive span and reduced adult feeding rate can increase colony fitness, potentially by reducing futile food consumption. Early adult death was particularly beneficial when adult food consumption rate was high. These results imply that programmed, adaptive death could promote colony fitness in C. elegans through a consumer sacrifice mechanism. Thus, C. elegans lifespan may be limited not by aging in the usual sense but rather by apoptosis-like programmed death.

HLH-30/TFEB Is a Master Regulator of Reproductive Quiescence

Birgit Gerisch [1], Rebecca George Tharyan [1], Jennifer Mak [1], Sarah I. Denzel [1, 2], Till Popkes-van Oepen [1, 2], Nadine Henn [1], Adam Antebi [1, 2, 3]

All animals have evolved the ability to survive nutrient deprivation, and nutrient signaling pathways are conserved modulators of health and disease. In *C. elegans*, late-larval starvation provokes the adult reproductive diapause (ARD), a long-lived quiescent state that enables survival for months without food, yet underlying molecular mechanisms remain unknown. Here, we show that ARD is distinct from other forms of diapause, showing little requirement for canonical longevity pathways, autophagy, and fat metabolism. Instead it requires the HLH-30/TFEB transcription factor to promote the morphological and physiological remodeling involved in ARD entry, survival, and recovery, suggesting that HLH-30 is a master regulator of reproductive quiescence. HLH-30 transcriptome and genetic analyses reveal that Max-like HLH factors, AMP-kinase, mTOR, protein synthesis, and mitochondrial fusion are target processes that promote ARD longevity. ARD thus rewires metabolism to ensure long-term survival and may illuminate similar mechanisms acting in stem cell quiescence and long-term fasting.

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J Vis Exp. 2020 Mar 27;(157). doi: 10.3791/61004.

Characterization of Amyloid Structures in Aging C. Elegans Using Fluorescence Lifetime Imaging.

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⊕ Author information

Abstract

Amyloid fibrils are associated with a number of neurodegenerative diseases such as Huntington's, Parkinson's, or Alzheimer's disease. These amyloid fibrils can sequester endogenous metastable proteins as well as components of the proteostasis network (PN) and thereby exacerbate protein misfolding in the cell. There are a limited number of tools available to assess the aggregation process of amyloid proteins within an animal. We present a protocol for fluorescence lifetime microscopy (FLIM) that allows monitoring as well as quantification of the amyloid fibrilization in specific cells, such as neurons, in a noninvasive manner and with the progression of aging and upon perturbation of the PN. FLIM is independent of the expression levels of the fluorophore and enables an analysis of the aggregation process without any further staining or bleaching. Fluorophores are quenched when they are in close vicinity of amyloid structures, which results in a decrease of the fluorescence lifetime. The quenching directly correlates with the aggregation of the amyloid protein. FLIM is a versatile technique that can be applied to compare the fibrilization process of different amyloid proteins, environmental stimuli, or genetic backgrounds in vivo in a non-invasive manner.

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Bacterially produced metabolites protect C. elegans neurons from degeneration.

Urrutia A[1,2], García-Angulo VA[2,3], Fuentes A[2], Caneo M[1,2], Legüe M[1,2], Urquiza S[2], Delgado SE[1,2], Ugalde J[2], Burdisso P[4], Calixto A[1,2].

⊕ Author information

Abstract

Caenorhabditis elegans and its cognate bacterial diet comprise a reliable, widespread model to study diet and microbiota effects on host physiology. Nonetheless, how diet influences the rate at which neurons die remains largely unknown. A number of models have been used in C. elegans as surrogates for neurodegeneration. One of these is a C. elegans strain expressing a neurotoxic allele of the mechanosensory abnormality protein 4 (MEC-4d) degenerin/epithelial Na+ (DEG/ENaC) channel, which causes the progressive degeneration of the touch receptor neurons (TRNs). Using this model, our study evaluated the effect of various dietary bacteria on neurodegeneration dynamics. Although degeneration of TRNs was steady and completed at adulthood in the strain routinely used for C. elegans maintenance (Escherichia coli OP50), it was significantly reduced in environmental and other laboratory bacterial strains. Strikingly, neuroprotection reached more than 40% in the E. coli HT115 strain. HT115 protection was long lasting well into old age of animals and was not restricted to the TRNs. Small amounts of HT115 on OP50 bacteria as well as UV-killed HT115 were still sufficient to produce neuroprotection. Early growth of worms in HT115 protected neurons from degeneration during later growth in OP50. HT115 diet promoted the nuclear translocation of DAF-16 (ortholog of the FOXO family of transcription factors), a phenomenon previously reported to underlie neuroprotection caused by down-regulation of the insulin receptor in this system. Moreover, a daf-16 loss-of-function mutation abolishes HT115-driven neuroprotection. Comparative genomics, transcriptomics, and metabolomics approaches pinpointed the neurotransmitter γ-aminobutyric acid (GABA) and lactate as metabolites differentially produced between E. coli HT115 and OP50. HT115 mutant lacking glutamate decarboxylase enzyme genes (gad), which catalyze the conversion of GABA from glutamate, lost the ability to produce GABA and also to stop neurodegeneration. Moreover, in situ GABA supplementation or heterologous expression of glutamate decarboxylase in E. coli OP50 conferred neuroprotective activity to this strain. Specific C. elegans GABA transporters and receptors were required for full HT115-mediated neuroprotection. Additionally, lactate supplementation also increased anterior ventral microtubule (AVM) neuron survival in OP50. Together, these results demonstrate that bacterially produced GABA and other metabolites exert an effect of neuroprotection in the host, highlighting the role of neuroactive compounds of the diet in nervous system homeostasis.

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Novel diets as nutraceuticals to alter lifespan and healthspan trajectories in *C. elegans*

Nicole L Stuhr, Sean P Curran

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Abstract

Diet is one of the more variable aspects in life due to the variety of options that organisms are exposed to in their natural habitats. In the laboratory, *C. elegans* are raised on bacterial monocultures, traditionally the *E.coli* B strain OP50, and spontaneously occurring microbial contaminants are removed to limit experimental variability because diet - including the presence of contaminants, can exert a potent influence over animal physiology. In order to diversify the menu available to culture *C. elegans* in the lab, we have isolated and cultured three such microbes: *Methylobacterium*, *Xanthomonas*, and *Sphingomonas*. The nutritional composition of these diets is unique, and when fed to *C. elegans*, can differentially alter multiple life history traits including development, reproduction, and metabolism. In light of the influence each diet has on specific physiological attributes, we comprehensively assessed the impact of these diets on animal health and devised a blueprint for utilizing different diet combinations over the lifespan, as a nutraceutical for optimal longevity. The expansion of the bacterial diet options to use in the laboratory will provide a critical tool to better understand the complexities of gene-diet interactions for health.

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Axin-mediated regulation of lifespan and muscle health in *C. elegans* involves AMPK-FOXO signaling

Avijit Mallick, Bhagwati P Gupta

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SUMMARY

Aging is a significant risk factor for several diseases. Studies have uncovered multiple signaling pathways that modulate the process of aging including the Insulin/IGF-1 signaling (IIS). In *C. elegans* the key regulator of IIS is DAF-16/FOXO whose activity is regulated by phosphorylation. A major kinase involved in DAF-16-mediated lifespan extension is the AMPK catalytic subunit homolog, AAK-2. In this study, we demonstrate a novel role of PRY-1/Axin in AAK-2 activation to regulate DAF-16 function. The *pry-1* transcriptome contains many genes associated with aging and muscle function. Consistent with this, *pry-1* is strongly expressed in muscles and muscle-specific overexpression of *pry-1* extends the lifespan, delays muscle aging, and improves mitochondrial morphology in DAF-16-dependent manner. Furthermore, PRY-1 is necessary for AAK-2 phosphorylation. Together, our data demonstrate a crucial role of PRY-1 in maintaining the lifespan and muscle health. Since muscle health declines with age, our study offers new possibilities to manipulate Axin function to delay muscle aging and improve lifespan.

REVIEWS/COMMENTS/ METHODS/EDITORIALS

Strategies to Prevent or Remediate Cancer and Treatment-Related Aging FREE

Up to 85% of adult cancer survivors and 99% of adult survivors of childhood cancer live with an accumulation of chronic conditions, frailty, and/or cognitive impairments resulting from cancer and its treatment. Thus, survivors often show an accelerated development of multiple geriatric syndromes and need therapeutic interventions. To advance progress in this area, the National Cancer Institute convened the second of two think tanks under the auspices of the Cancer and Accelerated Aging: Advancing Research for Healthy Survivors initiative. Experts assembled to share evidence of promising strategies to prevent, slow, or reverse the aging consequences of cancer and its treatment. The meeting identified research and resource needs, including geroscience-guided clinical trials; comprehensive assessments of functional, cognitive, and psychosocial vulnerabilities to assess and predict age-related outcomes; preclinical and clinical research to determine the optimal dosing for behavioral (e.g., diet, exercise) and pharmacologic (e.g., senolytic) therapies; healthcare delivery research to evaluate the efficacy of integrated cancer care delivery models; optimization of intervention implementation, delivery, and uptake; and patient/provider education on cancer and treatment-related late and long-term adverse effects. Addressing these needs will expand knowledge of aging-related consequences of cancer and cancer treatment and inform strategies to promote healthy aging of cancer survivors.

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Benefits of Metformin in Attenuating the Hallmarks of Aging

Ameya S. Kulkarni [1, 2], Sriram Gubbi [3], Nir Barzilai [1, 2]

Biological aging involves an interplay of conserved and targetable molecular mechanisms, summarized as the hallmarks of aging. Metformin, a biguanide that combats age-related disorders and improves health span, is the first drug to be tested for its age-targeting effects in the large clinical trial—TAME (targeting aging by metformin). This review focuses on metformin's mechanisms in attenuating hallmarks of aging and their interconnectivity, by improving nutrient sensing, enhancing autophagy and intercellular communication, protecting against macromolecular damage, delaying stem cell aging, modulating mitochondrial function, regulating transcription, and lowering telomere attrition and senescence. These characteristics make metformin an attractive gerotherapeutic to translate to human trials.

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Biohorology and biomarkers of aging: current state-of-the-art, challenges and opportunities

Fedor Galkin [a], Polina Mamoshina [b, c], Aleksandr Aliper [a], João Pedro de Magalhães [d, g], Vadim N. Gladyshev [e, f], Alex Zhavoronkov [a, g, h]

The aging process results in multiple traceable footprints, which can be quantified and used to estimate an organism's age. Examples of such aging biomarkers include epigenetic changes, telomere attrition, and alterations in gene expression and metabolite concentrations. More than a dozen aging clocks use molecular features to predict an organism's age, each of them utilizing different data types and training procedures. Here, we offer a detailed comparison of existing mouse and human aging clocks, discuss their technological limitations and the underlying machine learning algorithms. We also discuss promising future directions of research in biohorology — the science of measuring the passage of time in living systems. Overall, we expect deep learning, deep neural networks and generative approaches to be the next power tools in this timely and actively developing field.

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Aging Biomarkers: From Functional Tests to Multi-Omics Approaches

Ksenia S. Kudryashova, Ksenia Burka, Anton Y. Kulaga, Nataliya S. Vorobyeva, Brian K. Kennedy

Aging results in various deleterious changes in the human body that may lead to loss of function and the manifestation of chronic diseases. While diseases can generally be reliably diagnosed, the aging process itself requires more sophisticated approaches to evaluate its progression. Numerous attempts have been made to establish biomarkers to quantify human aging at the cellular, tissue, and organismal level. Here, an up-to-date overview of biomarkers related to human aging with an emphasis on biomarkers that take into account different mechanisms of aging between individuals is provided. Classical discrete molecular and non-molecular biomarkers handpicked by researches on the base of their strong correlation with age, as well as emerging omics-based biomarkers, are discussed and potential future directions and developments in the field of aging assessment are outlined.

Reducing Senescent Cell Burden in Aging and Disease

Cellular senescence is a primary aging process and tumor suppressive mechanism characterized by irreversible growth arrest, apoptosis resistance, production of a senescence-associated secretory phenotype (SASP), mitochondrial dysfunction, and alterations in DNA and chromatin. In preclinical aging models, accumulation of senescent cells is associated with multiple chronic diseases and disorders, geriatric syndromes, multimorbidity, and accelerated aging phenotypes. In animals, genetic and pharmacologic reduction of senescent cell burden results in the prevention, delay, and/or alleviation of a variety of aging-related diseases and sequelae. Early clinical trials have thus far focused on safety and target engagement of senolytic agents that clear senescent cells. We hypothesize that these pharmacologic interventions may have transformative effects on geriatric medicine.

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Targeting senescent cells to attenuate cardiovascular disease progression

Cardiovascular disease (CVD) is the most common disease to increase as life expectancy increases. Most high-profile pharmacological treatments for age-related CVD have led to inefficacious results, implying that novel approaches to treating these pathologies are needed. Emerging data have demonstrated that senescent cardiovascular cells, which are characterized by irreversible cell cycle arrest and a distinct senescence-associated secretory phenotype, accumulate in aged or diseased cardiovascular systems, suggesting that they may impair cardiovascular function. This review discusses the evidence implicating senescent cells in cardiovascular ageing, the onset and progression of CVD, and the molecular mechanisms underlying cardiovascular cell senescence. We also review eradication of senescent cardiovascular cells by small-molecule-drug–mediated apoptosis and immune cell-mediated efferocytosis and toxicity as promising and precisely targeted therapeutics for CVD prevention and treatment.

Mitochondria as intracellular signaling platforms in health and disease

Jay X. Tan, Toren Finkel

Mitochondria, long viewed solely in the context of bioenergetics, are increasingly emerging as critical hubs for intracellular signaling. Due to their bacterial origin, mitochondria possess their own genome and carry unique lipid components that endow these organelles with specialized properties to help orchestrate multiple signaling cascades. Mitochondrial signaling modulates diverse pathways ranging from metabolism to redox homeostasis to cell fate determination. Here, we review recent progress in our understanding of how mitochondria serve as intracellular signaling platforms with a particular emphasis on lipid-mediated signaling, innate immune activation, and retrograde signaling. We further discuss how these signaling properties might potentially be exploited to develop new therapeutic strategies for a range of age-related conditions.

Evolutionary Conservation of Transcription Factors Affecting Longevity

The increasing number of older people is resulting in an increased prevalence of age-related diseases. Research has shown that the ageing process itself is a potential point of intervention. Indeed, gene expression can be optimised for health in older ages through manipulation of transcription factor (TF) activity. This review is focused on the ever-growing number of TFs whose effects on ageing are evolutionarily conserved. These regulate a plethora of functions, including stress resistance, metabolism, and growth. They are engaged in complex interactions within and between different cell types, impacting the physiology of the entire organism. Since ageing is not programmed, the conservation of their effects on lifespan is most likely a reflection of the conservation of their functions in youth.

Neuroimmune Connections in Aging and Neurodegenerative Diseases

In recent years, the inter-relationship between the innate immune system and the central nervous system (CNS) has moved to the forefront of biomedical research, with the discovery that these two physiological systems modulate each other by a steady mutual interaction. During normal brain aging, but also under certain pathological conditions, this crosstalk can go beyond physiological control, resulting in an unresolved inflammatory response of the CNS-resident immune cells that might initiate and propagate the progression of severe tissue damage and neurodegeneration. In this review, we focus on the impact of CNS-resident cells of the innate immune system for the development of neurodegenerative diseases, review immune pathway genes that have been identified, and discuss the vicious cycle between inflammation and neurodegeneration.

Polyunsaturated Fatty Acid Deuteration against Neurodegeneration ☆

Mikhail S. Shchepinov [1]

Oxidative stress is a common feature of genetic and idiopathic neurological diseases that thus far have been intractable to drug therapy. Polyunsaturated fatty acids (PUFAs) form cellular, mitochondrial, retinal, and other membranes highly important in neuronal function. However, PUFAs are susceptible to the noxious lipid peroxidation (LPO) chain reaction, which is a common feature of various neurological and age-related pathologies, making this pathway an attractive target for therapeutic intervention. Regioselective deuteration that reinforces oxidation-prone, bis-allylic sites of PUFAs is a novel, nonantioxidant treatment modality that dramatically reduces LPO, potentially mitigating numerous diseases through preservation of membrane properties and amelioration of oxidative stress. Animal disease models and several ongoing human clinical trials highlight the potential of the deuterated-PUFA (D-PUFA) drug candidates currently in development.

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Hitchhiking on vesicles; a way to harness age-related proteopathies?

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Author information

Abstract

Central to proteopathies and leading to most age-related neurodegenerative disorders is a failure in protein quality control (PQC). To harness the toxicity of misfolded and damaged disease proteins, such proteins are either refolded, degraded by temporal PQC or sequestered by spatial PQC into specific, organelle-associated, compartments within the cell. Here, we discuss the impact of vesicle trafficking pathways in general, and syntaxin 5 in particular, as key players in spatial PQC directing misfolded proteins to the surface of vacuole and mitochondria, which facilitates their clearance and detoxification. Since boosting vesicle trafficking genetically can positively impact on spatial PQC and make cells less sensitive to misfolded disease proteins, we speculate that regulators of such trafficking might serve as therapeutic targets for age-related neurological disorders.

OTHER RESEARCH & REVIEWS

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PathBank: a comprehensive pathway database for model organisms

PathBank (www.pathbank.org) is a new, comprehensive, visually rich pathway database containing more than 110 000 machine-readable pathways found in 10 model organisms (*Homo sapiens, Bos taurus, Rattus norvegicus, Mus musculus, Drosophila melanogaster, Caenorhabditis elegans, Arabidopsis thaliana, Saccharomyces cerevisiae, Escherichia coli* and *Pseudomonas aeruginosa*). PathBank aims to provide a pathway for every protein and a map for every metabolite. This resource is designed specifically to support pathway elucidation and pathway discovery in transcriptomics, proteomics, metabolomics and systems biology. It provides detailed, fully searchable, hyperlinked diagrams of metabolic, metabolite signaling, protein signaling, disease, drug and physiological pathways. All PathBank pathways include information on the relevant organs, organelles, subcellular compartments, cofactors, molecular locations, chemical structures and protein quaternary structures. Each small molecule is hyperlinked to the rich data contained in public chemical databases such as HMDB or DrugBank and each protein or enzyme complex is hyperlinked to UniProt. All PathBank pathways are accompanied with references and detailed descriptions which provide an overview of the pathway, condition or processes depicted in each diagram. Every PathBank pathway is downloadable in several machine-readable and image formats including BioPAX, SBML, PWML, SBGN, RXN, PNG and SVG. PathBank also supports community annotations and submissions through the web-based PathWhiz pathway illustrator. The vast majority of PathBank's pathways (>95%) are not found in any other public pathway database.

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A reference map of the human binary protein interactome

Global insights into cellular organization and genome function require comprehensive understanding of the interactome networks that mediate genotype–phenotype relationships[1,2]. Here we present a human 'all-by-all' reference interactome map of human binary protein interactions, or 'HuRI'. With approximately 53,000 protein–protein interactions, HuRI has approximately four times as many such interactions as there are high-quality curated interactions from small-scale studies. The integration of HuRI with genome[3], transcriptome[4] and proteome[5] data enables cellular function to be studied within most physiological or pathological cellular contexts. We demonstrate the utility of HuRI in identifying the specific subcellular roles of protein–protein interactions. Inferred tissue-specific networks reveal general principles for the formation of cellular context-specific functions and elucidate potential molecular mechanisms that might underlie tissue-specific phenotypes of Mendelian diseases. HuRI is a systematic proteome-wide reference that links genomic variation to phenotypic outcomes.

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The Resurrection of Phenotypic Drug Discovery

Wayne E. Childers, Khaled M. Elokely and Magid Abou-Gharbia*

Prior to genetic mapping, the majority of drug discovery efforts involved phenotypic screening, wherein compounds were screened in either in vitro or in vivo models thought to mimic the disease state of interest. While never completely abandoning phenotypic approaches, the labor intensive nature of such tests encouraged the pharmaceutical industry to move away from them in favor of target-based drug discovery, which facilitated throughput and allowed for the efficient screening of large numbers of compounds. However, a consequence of reliance on target-based screening was an increased number of failures in clinical trials due to poor correlation between novel mechanistic targets and the actual disease state. As a result, the field has seen a recent resurrection in phenotypic drug discovery approaches. In this work, we highlight some recent phenotypic projects from our industrial past and in our current academic drug discovery environment that have provided encouraging results.

Comprehensive Map of the Regulated Cell Death Signaling Network: A Powerful Analytical Tool for Studying Diseases

The processes leading to, or avoiding cell death are widely studied, because of their frequent perturbation in various diseases. Cell death occurs in three highly interconnected steps: Initiation, signaling and execution. We used a systems biology approach to gather information about all known modes of regulated cell death (RCD). Based on the experimental data retrieved from literature by manual curation, we graphically depicted the biological processes involved in RCD in the form of a seamless comprehensive signaling network map. The molecular mechanisms of each RCD mode are represented in detail. The RCD network map is divided into 26 functional modules that can be visualized contextually in the whole seamless network, as well as in individual diagrams. The resource is freely available and accessible via several web platforms for map navigation, data integration, and analysis. The RCD network map was employed for interpreting the functional differences in cell death regulation between Alzheimer's disease and non-small cell lung cancer based on gene expression data that allowed emphasizing the molecular mechanisms underlying the inverse comorbidity between the two pathologies. In addition, the map was used for the analysis of genomic and transcriptomic data from ovarian cancer patients that provided RCD map-based signatures of four distinct tumor subtypes and highlighted the difference in regulations of cell death molecular mechanisms. View Full-Text

Fatal heart disease among cancer patients

Kelsey C. Stoltzfus, Ying Zhang, Kathleen Sturgeon, Lawrence I. Sinoway, Daniel M. Trifiletti, Vernon M. Chinchilli & Nicholas G. Zaorsky

As the overlap between heart disease and cancer patients increases as cancer-specific mortality is decreasing and the surviving population is aging, it is necessary to identify cancer patients who are at an increased risk of death from heart disease. The purpose of this study is to identify cancer patients at highest risk of fatal heart disease compared to the general population and other cancer patients at risk of death during the study time period. Here we report that 394,849 of the 7,529,481 cancer patients studied died of heart disease. The heart disease-specific mortality rate is 10.61/10,000-person years, and the standardized mortality ratio (SMR) of fatal heart disease is 2.24 (95% CI: 2.23–2.25). Compared to other cancer patients, patients who are older, male, African American, and unmarried are at a greatest risk of fatal heart disease. For almost all cancer survivors, the risk of fatal heart disease increases with time.

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Cystine transporter regulation of pentose phosphate pathway dependency and disulfide stress exposes a targetable metabolic vulnerability in cancer

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SLC7A11-mediated cystine uptake is critical for maintaining redox balance and cell survival. Here we show that this comes at a significant cost for cancer cells with high levels of SLC7A11. Actively importing cystine is potentially toxic due to its low solubility, forcing cancer cells with high levels of SLC7A11 (SLC7A11^{high}) to constitutively reduce cystine to the more soluble cysteine. This presents a significant drain on the cellular NADPH pool and renders such cells dependent on the pentose phosphate pathway. Limiting glucose supply to SLC7A11^{high} cancer cells results in marked accumulation of intracellular cystine, redox system collapse and rapid cell death, which can be rescued by treatments that prevent disulfide accumulation. We further show that inhibitors of glucose transporters selectively kill SLC7A11^{high} cancer cells and suppress SLC7A11^{high} tumour growth. Our results identify a coupling between SLC7A11-associated cystine metabolism and the pentose phosphate pathway, and uncover an accompanying metabolic vulnerability for therapeutic targeting in SLC7A11^{high} cancers.

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Unprovoked Stabilization and Nuclear Accumulation of the Naked Mole-Rat p53 Protein

The naked mole-rat is a subterranean rodent, approximately the size of a mouse, renowned for its exceptional longevity (>30 years) and remarkable resistance to cancer. To explore putative mechanisms underlying the cancer resistance of the naked mole-rat, we investigated the regulation and function of the most commonly mutated tumor suppressor, TP53, in the naked mole-rat. We found that the p53 protein in naked mole-rat embryonic fibroblasts (NEFs) exhibits a half-life more than ten times in excess of the protein's characterized half-life in mouse and human embryonic fibroblasts. We determined that the long half-life of the naked mole-rat p53 protein reflects protein-extrinsic regulation. Relative to mouse and human p53, a larger proportion of naked mole-rat p53 protein is constitutively localized in the nucleus prior to DNA damage. Nevertheless, DNA damage is sufficient to induce activation of canonical p53 target genes in NEFs. Despite the uniquely long half-life and unprecedented basal nuclear localization of p53 in NEFs, naked mole-rat p53 retains its canonical tumor suppressive activity. Together, these findings suggest that the unique stabilization and regulation of the p53 protein may contribute to the naked mole-rat's remarkable resistance to cancer.

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Partial impairment of insulin receptor expression mimics fasting to prevent diet-induced fatty liver disease

Excessive insulin signaling through the insulin receptor (IR) may play a role in the pathogenesis of diet-induced metabolic disease, including obesity and type 2 diabetes. Here we investigate whether heterozygous impairment of insulin receptor (IR) expression limited to peripheral, i.e. non-CNS, tissues of adult mice impacts the development of high-fat diet-induced metabolic deterioration. While exhibiting some features of insulin resistance, PerIRKO$^{+/-}$ mice display a hepatic energy deficit accompanied by induction of energy-sensing AMPK, mitochondrial biogenesis, PPARα, unexpectedly leading to protection from, and reversal of hepatic lipid accumulation (steatosis hepatis, NAFLD). Consistently, and unlike in control mice, the PPARα activator fenofibrate fails to further affect hepatic lipid accumulation in PerIRKO$^{+/-}$ mice. Taken together, and opposing previously established diabetogenic features of insulin resistance, incomplete impairment of insulin signaling may mimic central aspects of calorie restriction to limit hepatic lipid accumulation during conditions of metabolic stress.

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Discovery of a Cyclic Choline Analog That Inhibits Anaerobic Choline Metabolism by Human Gut Bacteria

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The anaerobic conversion of choline to trimethylamine (TMA) by the human gut microbiota has been linked to multiple human diseases. The potential impact of this microbial metabolic activity on host health has inspired multiple efforts to identify small molecule inhibitors. Here, we use information about the structure and mechanism of the bacterial enzyme choline TMA-lyase (CutC) to develop a cyclic choline analog that inhibits the conversion of choline to TMA in bacterial whole cells and in a complex gut microbial community. *In vitro* biochemical assays and a crystal structure suggest that this analog is a competitive, mechanism-based inhibitor. This work demonstrates the utility of structure-based design to access inhibitors of radical enzymes from the human gut microbiota.

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MG-HCr, the Methylglyoxal-Derived Hydroimidazolone of Creatine, a Biomarker for the Dietary Intake of Animal Source Food

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In the course of the Maillard reaction *in vivo* or in food, creatine reacts with the 1,2-dicarbonyl compound methylglyoxal to *N*-(4-methyl-5-oxo-1-imidazolin-2-yl)sarcosine (MG-HCr). We studied whether the urinary excretion of MG-HCr is affected by its intake with meat or by the intake of creatine and subsequent *in vivo* formation of MG-HCr. Therefore, 24 h urine of 30 subjects with different dietary habits was analyzed with HPLC-MS/MS. The daily MG-HCr excretion via urine varied between omnivores (0.39–9.67 μmol/day, n = 24), vegetarians (0.18–0.97 μmol/day, n = 19), and vegans (0.10–0.27 μmol/day, n = 8). An intervention study with 18 subjects demonstrated the bioavailability of MG-HCr (ca. 54%) from 200 g of heated meat and its quick excretion with urine. A creatine intervention of 0.44 g did not increase MG-HCr excretion. Thus, the differences in MG-HCr excretion between different diets are mainly caused by the dietary uptake of MG-HCr. We additionally found MG-HCr in milk and egg products, where it is formed during heat treatment. This partly explains differences in MG-HCr excretion of vegetarians and vegans. Hence, MG-HCr in urine is a short-term marker for the intake of heat-processed animal source food.