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Scientific News
5th of April 2020
Sven Bulterijs

Business/Conferences/ General news

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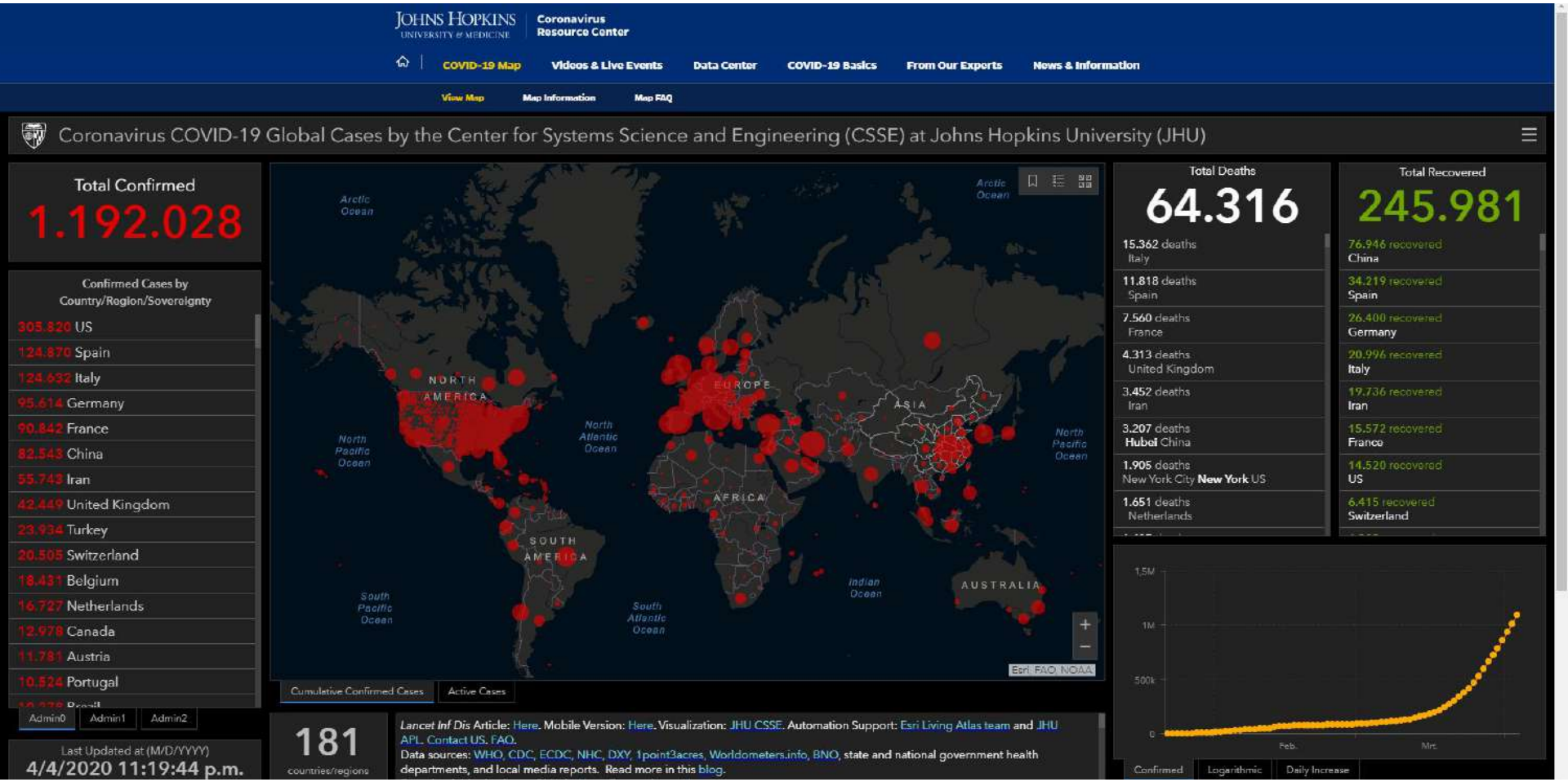

In one nursing home in Antwerp 25% of residents and 21% of staff was found to be infected with SARS-CoV-2!

Alarmerende cijfers tests in woonzorgcentra "besmettingen gaan door zonder dat we het beseffen"

't Zand | Coronavirus | Covid19 | Woonzorgcentra

Embed

Enkele Antwerpse Woonzorgcentra zijn op eigen initiatief hun bewoners en zorgpersoneel beginnen testen op Covid-19 omdat testen van de overheid uitblijven en dat levert opmerkelijke resultaten op. In woonzorgcentrum 't Zand op Linkeroever bijvoorbeeld testte minstens 25 procent van de bewoners en 21 procent van het personeel woensdag positief op corona.

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Respiratory virus shedding in exhaled breath and efficacy of face masks

We identified seasonal human coronaviruses, influenza viruses and rhinoviruses in exhaled breath and coughs of children and adults with acute respiratory illness. Surgical face masks significantly reduced detection of influenza virus RNA in respiratory droplets and coronavirus RNA in aerosols, with a trend toward reduced detection of coronavirus RNA in respiratory droplets. Our results indicate that surgical face masks could prevent transmission of human coronaviruses and influenza viruses from symptomatic individuals.

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The proximal origin of SARS-CoV-2

Kristian G. Andersen ✉, Andrew Rambaut, W. Ian Lipkin, Edward C. Holmes & Robert F. Garry

Nature Medicine (2020) | Cite this article

To the Editor — Since the first reports of novel pneumonia (COVID-19) in Wuhan, Hubei province, China[1,2], there has been considerable discussion on the origin of the causative virus, SARS-CoV-2[3] (also referred to as HCoV-19)[4]. Infections with SARS-CoV-2 are now widespread, and as of 11 March 2020, 121,564 cases have been confirmed in more than 110 countries, with 4,373 deaths[5].

SARS-CoV-2 is the seventh coronavirus known to infect humans; SARS-CoV, MERS-CoV and SARS-CoV-2 can cause severe disease, whereas HKU1, NL63, OC43 and 229E are associated with mild symptoms[6]. Here we review what can be deduced about the origin of SARS-CoV-2 from comparative analysis of genomic data. We offer a perspective on the notable features of the SARS-CoV-2 genome and discuss scenarios by which they could have arisen. Our analyses clearly show that SARS-CoV-2 is not a laboratory construct or a purposefully manipulated virus.

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A SARS-CoV-2-Human Protein-Protein Interaction Map Reveals Drug Targets and Potential Drug-Repurposing

An outbreak of the novel coronavirus SARS-CoV-2, the causative agent of COVID-19 respiratory disease, has infected over 290,000 people since the end of 2019, killed over 12,000, and caused worldwide social and economic disruption[1,2]. There are currently no antiviral drugs with proven efficacy nor are there vaccines for its prevention. Unfortunately, the scientific community has little knowledge of the molecular details of SARS-CoV-2 infection. To illuminate this, we cloned, tagged and expressed 26 of the 29 viral proteins in human cells and identified the human proteins physically associated with each using affinity-purification mass spectrometry (AP-MS), which identified 332 high confidence SARS-CoV-2-human protein-protein interactions (PPIs). Among these, we identify 67 druggable human proteins or host factors targeted by 69 existing FDA-approved drugs, drugs in clinical trials and/or preclinical compounds, that we are currently evaluating for efficacy in live SARS-CoV-2 infection assays. The identification of host dependency factors mediating virus infection may provide key insights into effective molecular targets for developing broadly acting antiviral therapeutics against SARS-CoV-2 and other deadly coronavirus strains.

Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial

Background

Chloroquine and hydroxychloroquine have been found to be efficient on SARS-CoV-2, and reported to be efficient in Chinese COV-19 patients. We evaluate the role of hydroxychloroquine on respiratory viral loads.

Patients and methods

French Confirmed COVID-19 patients were included in a single arm protocol from early March to March 16th, to receive 600mg of hydroxychloroquine daily and their viral load in nasopharyngeal swabs was tested daily in a hospital setting. Depending on their clinical presentation, azithromycin was added to the treatment. Untreated patients from another center and cases refusing the protocol were included as negative controls. Presence and absence of virus at Day6-post inclusion was considered the end point.

Results

Six patients were asymptomatic, 22 had upper respiratory tract infection symptoms and eight had lower respiratory tract infection symptoms.

Twenty cases were treated in this study and showed a significant reduction of the viral carriage at D6-post inclusion compared to controls, and much lower average carrying duration than reported of untreated patients in the literature. Azithromycin added to hydroxychloroquine was significantly more efficient for virus elimination.

Conclusion

Despite its small sample size our survey shows that hydroxychloroquine treatment is significantly associated with viral load reduction/disappearance in COVID-19 patients and its effect is reinforced by azithromycin.

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A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19)

Abstract

Objective: To evaluate the efficacy and safety of hydroxychloroquine (HCQ) in the treatment of patients with common coronavirus disease-19 (COVID-19). **Methods:** We prospectively enrolled 30 treatment-na?ve patients with confirmed COVID-19 after informed consent at Shanghai Public Health Clinical Center. The patients were randomized 1:1 to HCQ group and the control group. Patients in HCQ group were given HCQ 400 mg per day for 5 days plus conventional treatments, while those in the control group were given conventional treatment only. The primary endpoint was negative conversion rate of COVID-19 nucleic acid in respiratory pharyngeal swab on days 7 after randomization. This study has been approved by the ethics committee of Shanghai public health clinical center and registered online (NCT04261517). **Results:** One patient in HCQ group developed to severe during the treatment. On day 7, COVID-19 nucleic acid of throat swabs was negative in 13 (86.7%) cases in the HCQ group and 14 (93.3%) cases in the control group (P>0.05). The median duration from hospitalization to virus nucleic acid negative conservation was 4 (1-9) days in HCQ group, which is comparable to that in the control group[2 (1-4) days, (U=83.5, P>0.05)]. The median time for body temperature normalization in HCQ group was 1 (0-2) after hospitalization, which was also comparable to that in the control group 1 (0-3). Radiological progression was shown on CT images in 5 cases (33.3%) of the HCQ group and 7 cases (46.7%) of the control group, and all patients showed improvement in follow-up examination. Four cases (26.7%) of the HCQ group and 3 cases (20%) of the control group had transient diarrhea and abnormal liver function (P>0.05). **Conclusions:** The prognosis of common COVID-19 patients is good. Larger sample size study are needed to investigate the effects of HCQ in the treatment of COVID-19. Subsequent research should determine better endpoint and fully consider the feasibility of experiments such as sample size.

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Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial

Aims: Studies have indicated that chloroquine (CQ) shows antagonism against COVID-19 in vitro. However, evidence regarding its effects in patients is limited. This study aims to evaluate the efficacy of hydroxychloroquine (HCQ) in the treatment of patients with COVID-19. Main methods: From February 4 to February 28, 2020, 62 patients suffering from COVID-19 were diagnosed and admitted to Renmin Hospital of Wuhan University. All participants were randomized in a parallel-group trial, 31 patients were assigned to receive an additional 5-day HCQ (400 mg/d) treatment, Time to clinical recovery (TTCR), clinical characteristics, and radiological results were assessed at baseline and 5 days after treatment to evaluate the effect of HCQ. Key findings: For the 62 COVID-19 patients, 46.8% (29 of 62) were male and 53.2% (33 of 62) were female, the mean age was 44.7 (15.3) years. No difference in the age and sex distribution between the control group and the HCQ group. But for TTCR, the body temperature recovery time and the cough remission time were significantly shortened in the HCQ treatment group. Besides, a larger proportion of patients with improved pneumonia in the HCQ treatment group (80.6%, 25 of 32) compared with the control group (54.8%, 17 of 32). Notably, all 4 patients progressed to severe illness that occurred in the control group. However, there were 2 patients with mild adverse reactions in the HCQ treatment group. Significance: Among patients with COVID-19, the use of HCQ could significantly shorten TTCR and promote the absorption of pneumonia.

Limburgs bedrijf in poleposition voor medicijn tegen veroudering

Talloze biotechbedrijven overal ter wereld zijn in een wedren verwikkeld om het eerste medicijn op de markt te brengen dat veroudering vertraagt. Ann Beliën, zaakvoerster van het Limburgse Rejuvenate Biomed, maakt zich sterk dat zij die race zal winnen.

Ann Beliën uit Heusden-Zolder wil in 2022 het eerste middel ter wereld voorstellen dat veroudering aanpakt. "We hebben een grote voorsprong op de farmareuzen."
© Sven Dillen

Healthy Aging conference, Curaçao

Antilliaans Dagblad Maandag 9 maart 2020

Vlnr. Sandra Brouwer (UMCG), Dennis Arrindell (SVB), Helena van Haren (diëtiste Curaçao), Menno Reijneveld (UMCG), Sven Bulterijs (onderzoeker verjongingsbiotechnologie, Universiteit van Gent en Yale) en Algeron Haile (SVB). FOTO ELS KROON

zieningen, en de duurzaamheid op lange termijn van sociale verzekeringen. Hoogleraar gezondheidstechnologie aan het Universitair Medisch Centrum Groningen (UMCG) Erik Buskens, die wegens familieomstandigheden niet fysiek aanwezig kon zijn, hield zijn lezing via een door het bedrijf Sound & Vision tot stand gebrachte Skype-verbinding.

Conferences in 2020

EHA

Eurosymposium on Healthy Ageing

October 1-3, 2020
Brussels, Belgium

The 2020 Undoing Aging Conference is rescheduled to October (21-23)

3/12/2020

Aging research articles

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Transient non-integrative expression of nuclear reprogramming factors promotes multifaceted amelioration of aging in human cells

Aging is characterized by a gradual loss of function occurring at the molecular, cellular, tissue and organismal levels. At the chromatin level, aging associates with progressive accumulation of epigenetic errors that eventually lead to aberrant gene regulation, stem cell exhaustion, senescence, and deregulated cell/tissue homeostasis. Nuclear reprogramming to pluripotency can revert both the age and the identity of any cell to that of an embryonic cell. Recent evidence shows that transient reprogramming can ameliorate age-associated hallmarks and extend lifespan in progeroid mice. However, it is unknown how this form of rejuvenation would apply to naturally aged human cells. Here we show that transient expression of nuclear reprogramming factors, mediated by expression of mRNAs, promotes a rapid and broad amelioration of cellular aging, including resetting of epigenetic clock, reduction of the inflammatory profile in chondrocytes, and restoration of youthful regenerative response to aged, human muscle stem cells, in each case without abolishing cellular identity.

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Aging (Albany NY). 2020 Mar 11;12(5):4052-4066. doi: 10.18632/aging.102903. Epub 2020 Mar 11.

Survey of senescent cell markers with age in human tissues.

Idda ML[1,2], McClusky WG[1], Lodde V[1,3], Munk R[1], Abdelmohsen K[1], Rossi M[1], Gorospe M[1].

⊕ Author information

Abstract

Cellular senescence, triggered by sublethal damage, is characterized by indefinite growth arrest, altered gene expression patterns, and a senescence-associated secretory phenotype. While the accumulation of senescent cells during aging decreases tissue function and promotes many age-related diseases, at present there is no universal marker to detect senescent cells in tissues. Cyclin-dependent kinase inhibitors 2A (p16/CDKN2A) and 1A (p21/CDKN1A) can identify senescent cells, but few studies have examined the numbers of cells expressing these markers in different organs as a function of age. Here, we investigated systematically p16- and p21-positive cells in tissue arrays designed to include normal organs from persons across a broad spectrum of ages. Increased numbers of p21-positive and p16-positive cells with donor age were found in skin (epidermis), pancreas, and kidney, while p16-expressing cells increased in brain cortex, liver, spleen and intestine (colon), and p21-expressing cells increased in skin (dermis). The numbers of cells expressing p16 or p21 in lung did not change with age, and muscle did not appear to have p21- or p16-positive cells. In summary, different organs display different levels of the senescent proteins p16 and p21 as a function of age across the human life span.

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Observation of the Transport and Removal of Lipofuscin from the Mouse Myocardium using Transmission Electron Microscope

This study was performed to investigate whether the lipofuscin formed within cardiomyocytes can be excluded by the myocardial tissue. We have provided indicators that can be used for future studies on anti-aging interventions.

In the present study, the heart of a 5-month-old BALB/c mouse was obtained for resin embedding and ultra-thin sectioning. The specimens were observed under a Hitach 7500 transmission electron microscope, and the images were acquired using an XR401 side-insertion device.

Lipofuscin granules are found abundantly in myocardial cells. Cardiomyocytes can excrete lipofuscin granules into the myocardial interstitium using capsule-like protrusions that are formed on the sarcolemma. These granules enter the myocardial interstitium and can be de-aggregated to form "membrane-like garbage", which can pass from the myocardial stroma into the lumen of the vessel through its walls in the form of soluble fine particles through diffusion or endocytosis of capillaries. Smaller lipofuscin granules can pass through the walls of the vessels and enter the blood vessel lumen through the active transport function of the capillary endothelial cells. When the extended cytoplasmic end of macrophages and fibroblasts fuse with the endothelial cells, the lipofuscin granules or clumps found in the cells of the myocardial interstitium are transported to the capillary walls, and then, they are released into the lumen of the blood vessel by the endothelial cells.

The myocardial tissues of mice have the ability to eliminate the lipofuscin produced in the cardiomyocytes into the myocardial blood circulation. Although there are several mechanisms through which the myocardial tissues release lipofuscin into the bloodstream, it is mainly carried out in the form of small, fine, soluble, continuous transport.

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Temporal changes in the gene expression heterogeneity during brain development and aging

Cells in largely non-mitotic tissues such as the brain are prone to stochastic (epi-)genetic alterations that may cause increased variability between cells and individuals over time. Although increased inter-individual heterogeneity in gene expression was previously reported, whether this process starts during development or if it is restricted to the aging period has not yet been studied. The regulatory dynamics and functional significance of putative aging-related heterogeneity are also unknown. Here we address these by a meta-analysis of 19 transcriptome datasets from three independent studies, covering diverse human brain regions. We observed a significant increase in inter-individual heterogeneity during aging (20 + years) compared to postnatal development (0 to 20 years). Increased heterogeneity during aging was consistent among different brain regions at the gene level and associated with lifespan regulation and neuronal functions. Overall, our results show that increased expression heterogeneity is a characteristic of aging human brain, and may influence aging-related changes in brain functions.

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Differentiation drives widespread rewiring of the neural stem cell chaperone network

Neural stem and progenitor cells (NSPCs) are critical for continued cellular replacement in the adult brain. Life-long maintenance of a functional NSPC pool necessitates stringent mechanisms to preserve a pristine proteome. We find that the NSPCs chaperone network robustly maintains misfolded protein solubility and stress resilience through high levels of the ATP-dependent chaperonin TRiC/CCT. Strikingly, NSPC differentiation rewires the cellular chaperone network, reducing TRiC/CCT levels and inducing those of the ATP-independent small heat shock proteins (sHSPs). This switches the proteostasis strategy in neural progeny cells to promote sequestration of misfolded proteins into protective inclusions. The chaperone network of NSPCs is more effective than that of differentiated cells, leading to improved management of proteotoxic stress and amyloidogenic proteins. However, NSPC proteostasis is impaired by brain aging. The less efficient chaperone network of differentiated neural progeny may contribute to their enhanced susceptibility to neurodegenerative diseases characterized by aberrant protein misfolding and aggregation.

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The aging skin microenvironment dictates stem cell behavior

Aging manifests with architectural alteration and functional decline of multiple organs throughout an organism. In mammals, aged skin is accompanied by a marked reduction in hair cycling and appearance of bald patches, leading researchers to propose that hair follicle stem cells (HFSCs) are either lost, differentiate, or change to an epidermal fate during aging. Here, we employed single-cell RNA-sequencing to interrogate aging-related changes in the HFSCs. Surprisingly, although numbers declined, aging HFSCs were present, maintained their identity, and showed no overt signs of shifting to an epidermal fate. However, they did exhibit prevalent transcriptional changes particularly in extracellular matrix genes, and this was accompanied by profound structural perturbations in the aging SC niche. Moreover, marked age-related changes occurred in many nonepithelial cell types, including resident immune cells, sensory neurons, and arrector pili muscles. Each of these SC niche components has been shown to influence HF regeneration. When we performed skin injuries that are known to mobilize young HFSCs to exit their niche and regenerate HFs, we discovered that aged skin is defective at doing so. Interestingly, however, in transplantation assays in vivo, aged HFSCs regenerated HFs when supported with young dermis, while young HFSCs failed to regenerate HFs when combined with aged dermis. Together, our findings highlight the importance of SC:niche interactions and favor a model where youthfulness of the niche microenvironment plays a dominant role in dictating the properties of its SCs and tissue health and fitness.

The evolutionary dynamics and fitness landscape of clonal hematopoiesis

Abstract

Somatic mutations acquired in healthy tissues as we age are major determinants of cancer risk. Whether variants confer a fitness advantage or rise to detectable frequencies by chance remains largely unknown. Blood sequencing data from ~50,000 individuals reveal how mutation, genetic drift, and fitness shape the genetic diversity of healthy blood (clonal hematopoiesis). We show that positive selection, not drift, is the major force shaping clonal hematopoiesis, provide bounds on the number of hematopoietic stem cells, and quantify the fitness advantages of key pathogenic variants, at single-nucleotide resolution, as well as the distribution of fitness effects (fitness landscape) within commonly mutated driver genes. These data are consistent with clonal hematopoiesis being driven by a continuing risk of mutations and clonal expansions that become increasingly detectable with age.

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Endothelial mTOR maintains hematopoiesis during aging

Aging leads to a decline in hematopoietic stem and progenitor cell (HSPC) function. We recently discovered that aging of bone marrow endothelial cells (BMECs) leads to an altered crosstalk between the BMEC niche and HSPCs, that instructs young HSPCs to behave as aged HSPCs. Here, we demonstrate aging leads to a decrease in mTOR signaling within BMECs that potentially underlies the age-related impairment of their niche activity. Our findings reveal that pharmacological inhibition of mTOR using Rapamycin has deleterious effects on hematopoiesis. To formally determine whether endothelial-specific inhibition of mTOR can influence hematopoietic aging, we conditionally deleted mTOR in ECs ($mTOR^{(ECKO)}$) of young mice and observed that their HSPCs displayed attributes of an aged hematopoietic system. Transcriptional profiling of HSPCs from $mTOR^{(ECKO)}$ mice revealed that their transcriptome resembled aged HSPCs. Notably, during serial transplantations, exposure of wild type HSPCs to an $mTOR^{(ECKO)}$ microenvironment was sufficient to recapitulate aging-associated phenotypes, confirming the instructive role of EC-derived signals in governing HSPC aging.

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Sons accelerate maternal aging in a wild mammal

Aging, or senescence, is a progressive deterioration of physiological function with age. It leads to age-related declines in reproduction (reproductive senescence) and survival (actuarial senescence) in most organisms. However, senescence patterns can be highly variable across species, populations, and individuals, and the reasons for such variations remain poorly understood. Evolutionary theories predict that increases in reproductive effort in early life should be associated with accelerated senescence, but empirical tests have yielded mixed results. Although in sexually size-dimorphic species offspring of the larger sex (typically males) commonly require more parental resources, these sex differences are not currently incorporated into evolutionary theories of aging. Here, we show that female reproductive senescence varies with both the number and sex ratio of offspring weaned during early life, using data from a long-term study of bighorn sheep. For a given number of offspring, females that weaned more sons than daughters when aged between 2 and 7 y experienced faster senescence in offspring survival in old age. By contrast, analyses of actuarial senescence showed no cost of early-life reproduction. Our results unite two important topics in evolutionary biology: life history and sex allocation. Offspring sex ratio may help explain among-individual variation in senescence rates in other species, including humans.

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Sex differences in adult lifespan and aging rates of mortality across wild mammals

In human populations, women consistently outlive men, which suggests profound biological foundations for sex differences in survival. Quantifying whether such sex differences are also pervasive in wild mammals is a crucial challenge in both evolutionary biology and biogerontology. Here, we compile demographic data from 134 mammal populations, encompassing 101 species, to show that the female's median lifespan is on average 18.6% longer than that of conspecific males, whereas in humans the female advantage is on average 7.8%. On the contrary, we do not find any consistent sex differences in aging rates. In addition, sex differences in median adult lifespan and aging rates are both highly variable across species. Our analyses suggest that the magnitude of sex differences in mammalian mortality patterns is likely shaped by local environmental conditions in interaction with the sex-specific costs of sexual selection.

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The sex with the reduced sex chromosome dies earlier: a comparison across the tree of life

Many taxa show substantial differences in lifespan between the sexes. However, these differences are not always in the same direction. In mammals, females tend to live longer than males, while in birds, males tend to live longer than females. One possible explanation for these differences in lifespan is the unguarded X hypothesis, which suggests that the reduced or absent chromosome in the heterogametic sex (e.g. the Y chromosome in mammals and the W chromosome in birds) exposes recessive deleterious mutations on the other sex chromosome. While the unguarded X hypothesis is intuitively appealing, it had never been subject to a broad test. We compiled male and female longevity data for 229 species spanning 99 families, 38 orders and eight classes across the tree of life. Consistent with the unguarded X hypothesis, a meta-analysis showed that the homogametic sex, on average, lives 17.6% longer than the heterogametic sex. Surprisingly, we found substantial differences in lifespan dimorphism between female heterogametic species (in which the homogametic sex lives 7.1% longer) and male heterogametic species (in which the homogametic sex lives 20.9% longer). Our findings demonstrate the importance of considering chromosome morphology in addition to sexual selection and environment as potential drivers of sexual dimorphism, and advance our fundamental understanding of the mechanisms that shape an organism's lifespan.

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Genetic sex determination and sex-specific lifespan in tetrapods – evidence of a toxicY effect

Sex-specific lifespans are ubiquitous across the tree of life and exhibit broad taxonomic patterns that remain a puzzle, such as males living longer than females in birds and *vice versa* in mammals. The prevailing "unguarded-X" hypothesis (UXh) explains this by differential expression of recessive mutations in the X/Z chromosome of the heterogametic sex (e.g., females in birds and males in mammals), but has only received indirect support to date. An alternative hypothesis is that the accumulation of deleterious mutations and repetitive elements on the Y/W chromosome might lower the survival of the heterogametic sex ("toxic Y" hypothesis). Here, we report lower survival of the heterogametic relative to the homogametic sex across 138 species of birds, mammals, reptiles and amphibians, as expected if sex chromosomes shape sex-specific lifespans. We then analysed bird and mammal karyotypes and found that the relative sizes of the X and Z chromosomes are not associated with sex-specific lifespans, contrary to UXh predictions. In contrast, we found that Y size correlates negatively with male survival in mammals, where toxic Y effects are expected to be particularly strong. This suggests that small Y chromosomes benefit male lifespans. Our results confirm the role of sex chromosomes in explaining sex differences in lifespan, but indicate that, at least in mammals, this is better explained by "toxic Y" rather than UXh effects.

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Genomic analysis of male puberty timing highlights shared genetic basis with hair colour and lifespan

The timing of puberty is highly variable and is associated with long-term health outcomes. To date, understanding of the genetic control of puberty timing is based largely on studies in women. Here, we report a multi-trait genome-wide association study for male puberty timing with an effective sample size of 205,354 men. We find moderately strong genomic correlation in puberty timing between sexes (rg = 0.68) and identify 76 independent signals for male puberty timing. Implicated mechanisms include an unexpected link between puberty timing and natural hair colour, possibly reflecting common effects of pituitary hormones on puberty and pigmentation. Earlier male puberty timing is genetically correlated with several adverse health outcomes and Mendelian randomization analyses show a genetic association between male puberty timing and shorter lifespan. These findings highlight the relationships between puberty timing and health outcomes, and demonstrate the value of genetic studies of puberty timing in both sexes.

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Wild chimpanzees exhibit humanlike aging of glucocorticoid regulation

Cortisol, a key product of the stress response, has critical influences on degenerative aging in humans. In turn, cortisol production is affected by senescence of the hypothalamic–pituitary–adrenal (HPA) axis, leading to progressive dysregulation and increased cortisol exposure. These processes have been studied extensively in industrialized settings, but few comparative data are available from humans and closely related species living in natural environments, where stressors are very different. Here, we examine age-related changes in urinary cortisol in a 20-y longitudinal study of wild chimpanzees (n = 59 adults) in the Kanyawara community of Kibale National Park, Uganda. We tested for three key features of HPA aging identified in many human studies: increased average levels, a blunted diurnal rhythm, and enhanced response to stressors. Using linear mixed models, we found that aging was associated with a blunting of the diurnal rhythm and a significant linear increase in cortisol, even after controlling for changes in dominance rank. These effects did not differ by sex. Aging did not increase sensitivity to energetic stress or social status. Female chimpanzees experienced their highest levels of cortisol during cycling (versus lactation), and this effect increased with age. Male chimpanzees experienced their highest levels when exposed to sexually attractive females, but this effect was diminished by age. Our results indicate that chimpanzees share some key features of HPA aging with humans. These findings suggest that impairments of HPA regulation are intrinsic to the aging process in hominids and are side effects neither of extended human life span nor of atypical environments.

Cell Metab. 2020 Mar 16. pii: S1550-4131(20)30075-9. doi: 10.1016/j.cmet.2020.02.016. [Epub ahead of print]

Sugar-Induced Obesity and Insulin Resistance Are Uncoupled from Shortened Survival in Drosophila.

van Dam E[1], van Leeuwen LAG[1], Dos Santos E[1], James J[1], Best L[2], Lennicke C[1], Vincent AJ[1], Marinos G[2], Foley A[1], Buricova M[1], Mokochinski JB[1], Kramer HB[1], Lieb W[3], Laudes M[4], Franke A[5], Kaleta C[2], Cochemé HM[6].

⊕ Author information

Abstract

High-sugar diets cause thirst, obesity, and metabolic dysregulation, leading to diseases including type 2 diabetes and shortened lifespan. However, the impact of obesity and water imbalance on health and survival is complex and difficult to disentangle. Here, we show that high sugar induces dehydration in adult Drosophila, and water supplementation fully rescues their lifespan. Conversely, the metabolic defects are water-independent, showing uncoupling between sugar-induced obesity and insulin resistance with reduced survival in vivo. High-sugar diets promote accumulation of uric acid, an end-product of purine catabolism, and the formation of renal stones, a process aggravated by dehydration and physiological acidification. Importantly, regulating uric acid production impacts on lifespan in a water-dependent manner. Furthermore, metabolomics analysis in a human cohort reveals that dietary sugar intake strongly predicts circulating purine levels. Our model explains the pathophysiology of high-sugar diets independently of obesity and insulin resistance and highlights purine metabolism as a pro-longevity target.

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Aging Cell. 2020 Mar 20:e13124. doi: 10.1111/acel.13124. [Epub ahead of print]

Proteomic signatures of in vivo muscle oxidative capacity in healthy adults.

Adelnia F[1,2], Ubaida-Mohien C[1], Moaddel R[3], Shardell M[1], Lyashkov A[3], Fishbein KW[3], Aon MA[1], Spencer RG[3], Ferrucci L[1].

⊕ Author information

Abstract

Adequate support of energy for biological activities and during fluctuation of energetic demand is crucial for healthy aging; however, mechanisms for energy decline as well as compensatory mechanisms that counteract such decline remain unclear. We conducted a discovery proteomic study of skeletal muscle in 57 healthy adults (22 women and 35 men; aged 23-87 years) to identify proteins overrepresented and underrepresented with better muscle oxidative capacity, a robust measure of in vivo mitochondrial function, independent of age, sex, and physical activity. Muscle oxidative capacity was assessed by ^{31}P magnetic resonance spectroscopy postexercise phosphocreatine (PCr) recovery time (τ_{PCr}) in the vastus lateralis muscle, with smaller τ_{PCr} values reflecting better oxidative capacity. Of the 4,300 proteins quantified by LC-MS in muscle biopsies, 253 were significantly overrepresented with better muscle oxidative capacity. Enrichment analysis revealed three major protein clusters: (a) proteins involved in key energetic mitochondrial functions especially complex I of the electron transport chain, tricarboxylic acid (TCA) cycle, fatty acid oxidation, and mitochondrial ABC transporters; (b) spliceosome proteins that regulate mRNA alternative splicing machinery, and (c) proteins involved in translation within mitochondria. Our findings suggest that alternative splicing and mechanisms that modulate mitochondrial protein synthesis are central features of the molecular mechanisms aimed at maintaining mitochondrial function in the face of impairment. Whether these mechanisms are compensatory attempt to counteract the effect of aging on mitochondrial function should be further tested in longitudinal studies.

Aging (Albany NY). 2020 Mar 16;12. doi: 10.18632/aging.102872. [Epub ahead of print]

Transplant of microbiota from long-living people to mice reduces aging-related indices and transfers beneficial bacteria.

Chen Y[1], Zhang S[1], Zeng B[1], Zhao J[2], Yang M[1], Zhang M[1], Li Y[1], Ni Q[1], Wu[3], Li Y[1].

⊕ Author information

Abstract

A close relationship between age and gut microbiota exists in invertebrates and vertebrates, including humans. Long-living people are a model for studying healthy aging; they also have a distinctive microbiota structure. The relationship between the microbiota of long-living people and aging phenotype remains largely unknown. Herein, the feces of long-living people were transplanted into mice, which were then examined for aging-related indices and beneficial bacteria. Mice transplanted with fecal matter from long-living people (L group) had greater α diversity, more probiotic genera (*Lactobacillus* and *Bifidobacterium*), and short-chain fatty acid producing genera (*Roseburia, Faecalibacterium, Ruminococcus, Coprococcus*) than the control group. L group mice also accumulated less lipofuscin and β-galactosidase and had longer intestinal villi. This study indicates the effects that the gut microbiota from long-living people have on healthy aging.

Aging (Albany NY). 2020 Mar 3;12(5):4394-4406. doi: 10.18632/aging.102892. Epub 2020 Mar 3.

DNA methylation clocks as a predictor for ageing and age estimation in naked mole-rats, *Heterocephalus glaber*.

Lowe R[1], Danson AF[1], Rakyan VK[1,2], Yildizoglu S[1], Saldmann F[3,4], Viltard M[3], Friedlander G[4,5,6], Faulkes CG[7].

Author information

Abstract

The naked mole-rat, *Heterocephalus glaber* (NMR), the longest-lived rodent, is of significance and interest in the study of biomarkers for ageing. Recent breakthroughs in this field have revealed 'epigenetic clocks' that are based on the temporal accumulation of DNA methylation at specific genomic sites. Here, we validate the hypothesis of an epigenetic clock in NMRs based on changes in methylation of targeted CpG sites. We initially analysed 51 CpGs in NMR livers spanning an age range of 39-1,144 weeks and found 23 to be significantly associated with age ($p<0.05$). We then built a predictor of age using these sites. To test the accuracy of this model, we analysed an additional set of liver samples, and were successfully able to predict their age with a root mean squared error of 166 weeks. We also profiled skin samples with the same age range, finding a striking correlation between their predicted age versus their actual age ($R=0.93$), but which was lower when compared to the liver, suggesting that skin ages slower than the liver in NMRs. Our model will enable the prediction of age in wild-caught and captive NMRs of unknown age, and will be invaluable for further mechanistic studies of mammalian ageing.

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Mild depolarization of the inner mitochondrial membrane is a crucial component of an anti-aging program

The mitochondria of various tissues from mice, naked mole rats (NMRs), and bats possess two mechanistically similar systems to prevent the generation of mitochondrial reactive oxygen species (mROS): hexokinases I and II and creatine kinase bound to mitochondrial membranes. Both systems operate in a manner such that one of the kinase substrates (mitochondrial ATP) is electrophoretically transported by the ATP/ADP antiporter to the catalytic site of bound hexokinase or bound creatine kinase without ATP dilution in the cytosol. One of the kinase reaction products, ADP, is transported back to the mitochondrial matrix via the antiporter, again through an electrophoretic process without cytosol dilution. The system in question continuously supports H^+-ATP synthase with ADP until glucose or creatine is available. Under these conditions, the membrane potential, $\Delta\psi$, is maintained at a lower than maximal level (i.e., mild depolarization of mitochondria). This $\Delta\psi$ decrease is sufficient to completely inhibit mROS generation. In 2.5-y-old mice, mild depolarization disappears in the skeletal muscles, diaphragm, heart, spleen, and brain and partially in the lung and kidney. This age-dependent decrease in the levels of bound kinases is not observed in NMRs and bats for many years. As a result, ROS-mediated protein damage, which is substantial during the aging of short-lived mice, is stabilized at low levels during the aging of long-lived NMRs and bats. It is suggested that this mitochondrial mild depolarization is a crucial component of the mitochondrial anti-aging system.

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Illuminating NAD$^+$ Metabolism in Live Cells and In Vivo Using a Genetically Encoded Fluorescent Sensor.

Zou Y[1], Wang A[1], Huang L[2], Zhu X[3], Hu Q[2], Zhang Y[4], Chen X[2], Li F[4], Wang Q[2], Wang H[5], Liu R[2], Zuo F[2], Li T[2], Yao J[2], Qian Y[2], Shi M[2], Yue X[2], Chen W[2], Zhang Z[2], Wang C[6], Zhou Y[7], Zhu L[8], Ju Z[5], Loscalzo J[9], Yang Y[10], Zhao Y[11].

⊕ Author information

Abstract

Understanding of NAD$^+$ metabolism provides many critical insights into health and diseases, yet highly sensitive and specific detection of NAD$^+$ metabolism in live cells and in vivo remains difficult. Here, we present ratiometric, highly responsive genetically encoded fluorescent indicators, FiNad, for monitoring NAD$^+$ dynamics in living cells and animals. FiNad sensors cover physiologically relevant NAD$^+$ concentrations and sensitively respond to increases and decreases in NAD$^+$. Utilizing FiNad, we performed a head-to-head comparison study of common NAD$^+$ precursors in various organisms and mapped their biochemical roles in enhancing NAD$^+$ levels. Moreover, we showed that increased NAD$^+$ synthesis controls morphofunctional changes of activated macrophages, and directly imaged NAD$^+$ declines during aging in situ. The broad utility of the FiNad sensors will expand our mechanistic understanding of numerous NAD$^+$-associated physiological and pathological processes and facilitate screening for drug or gene candidates that affect uptake, efflux, and metabolism of this important cofactor.

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Blood pressure in frail older adults: associations with cardiovascular outcomes and all-cause mortality

Jane A H Masoli ✉, Joao Delgado, Luke Pilling, David Strain, David Melzer

Results

Risks of cardiovascular outcomes increased with SBPs >150 mmHg. Associations with mortality varied between non-frail <85 and frail 75–84-year-olds and all above 85 years. SBPs above the 130–139-mmHg reference were associated with lower mortality risk, particularly in moderate to severe frailty or above 85 years (e.g. 75–84 years: 150–159 mmHg Hazard Ratio (HR) mortality compared to 130–139: non-frail HR = 0.94, 0.92–0.97; moderate/severe frailty HR = 0.84, 0.77–0.92). SBP <130 mmHg and Diastolic(D)BP <80 mmHg were consistently associated with excess mortality, independent of BP trajectory toward the end of life.

Conclusions

In representative primary-care patients aged ≥75, BP <130/80 was associated with excess mortality. Hypertension was not associated with increased mortality at ages above 85 or at ages 75–84 with moderate/severe frailty, perhaps due to complexities of co-existing morbidities. The priority given to aggressive BP reduction in frail older people requires further evaluation.

C. elegans aging research

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Endogenous siRNAs promote proteostasis and longevity in germline less *C. elegans*.

Cohen-Berkman M[1], Dudkevich R[2], Ben-Hamo S[1], Fishman A[3], Salzberg Y[4], Waldman Ben-Asher H[1], Lamm AT[3], Henis-Korenblit S[2].

⊕ Author information

Abstract

How lifespan and the rate of aging are set is a key problem in biology. Small RNAs are conserved molecules that impact diverse biological processes through the control of gene expression. However, in contrast to miRNAs, the role of endo-siRNAs in aging remains unexplored. Here, by combining deep sequencing and genomic and genetic approaches in *C. elegans*, we reveal an unprecedented role for endo-siRNA molecules in the maintenance of proteostasis and lifespan extension in germline-less animals. Furthermore, we identify an endo-siRNA-regulated tyrosine phosphatase, which limits the longevity of germline-less animals by restricting the activity of the heat shock transcription factor HSF-1. Altogether, our findings point to endo-siRNAs as a link between germline removal and the HSF-1 proteostasis and longevity-promoting somatic pathway. This establishes a role for endo siRNAs in the aging process and identifies downstream genes and physiological processes that are regulated by the endo siRNAs to affect longevity.

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SKN-1 Is a Negative Regulator of DAF-16 and Somatic Stress Resistance in *Caenorhabditis elegans*

The transcription factor SKN-1, the *C. elegans* orthologue of mammalian Nrf protein, is a well-known longevity factor, and its activation is observed in several long-lived models. SKN-1 also plays essential roles in xenobiotic and oxidative stress responses. Here, we report deleterious functions of SKN-1 in somatic stress resistance that may impair lifespan. Constitutive SKN-1 activation impairs animal resistance to several stresses, including heat, ER stress and mitochondrial stress, which result from the suppression of DAF-16, another master regulator of longevity. SKN-1 activation abrogates DAF-16 nuclear import and downregulates DAF-16 target genes under stress conditions, while SKN-1 inhibition promotes the expression of DAF-16 targets, even in long-lived mutants. Further, SKN-1 activation induces the expression of vitellogenin proteins, which are required for SKN-1-mediated suppression of DAF-16 and stress resistance. Together, these findings identify detrimental roles for SKN-1 activation in animal health, and more importantly, inspire the rethinking of the complex roles for SKN-1 in aging regulation.

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Aging (Albany NY). 2020 Mar 24;12. doi: 10.18632/aging.102951. [Epub ahead of print]

Verapamil extends lifespan in *Caenorhabditis elegans* by inhibiting calcineurin activity and promoting autophagy.

Liu W[1], Lin H[1], Mao Z[1], Zhang L[1], Bao K[1], Jiang B[2], Xia C[3], Li W[4], Hu Z[1], Li J[1,3].

⊕ Author information

Abstract

Previous evidence has revealed that increase in intracellular levels of calcium promotes cellular senescence. However, whether calcium channel blockers (CCBs) can slow aging and extend lifespan is still unknown. In this study, we showed that verapamil, an L-type calcium channel blocker, extended the *Caenorhabditis elegans* (*C. elegans*) lifespan and delayed senescence in human lung fibroblasts. Verapamil treatment also improved healthspan in *C. elegans* as reflected by several age-related physiological parameters, including locomotion, thrashing, age-associated vulval integrity, and osmotic stress resistance. We also found that verapamil acted on the α1 subunit of an L-type calcium channel in *C. elegans*. Moreover, verapamil extended worm lifespan by inhibiting calcineurin activity. Furthermore, verapamil significantly promoted autophagy as reflected by the expression levels of LGG-1/LC3 and the mRNA levels of autophagy-related genes. In addition, verapamil could not further induce autophagy when *tax-6*, calcineurin gene, was knocked down, indicating that verapamil-induced lifespan extension is mediated via promoting autophagy processes downstream of calcineurin. In summary, our study provided mechanistic insights into the anti-aging effect of verapamil in *C. elegans*.

REVIEWS/COMMENTS/ METHODS/EDITORIALS

Aging Fits the Disease Criteria of the International Classification of Diseases

Khaltourina Daria [a] ✉, Matveyev Yuri [b], Alekseev Aleksey [c], Cortese Franco [d], Ioviţă Anca [e]

Abstract

The disease criteria used by the World Health Organization (WHO) were applied to human biological aging in order to assess whether aging can be classified as a disease. These criteria were developed for the 11th revision of the International Classification of Diseases (ICD) and included disease diagnostics, mechanisms, course and outcomes, known interventions, and linkage to genetic and environmental factors.

Results

Biological aging can be diagnosed with frailty indices, functional, blood-based biomarkers. A number of major causal mechanisms of human aging involved in various organs have been described, such as inflammation, replicative cellular senescence, immune senescence, proteostasis failures, mitochondrial dysfunctions, fibrotic propensity, hormonal aging, body composition changes, etc. We identified a number of clinically proven interventions, as well as genetic and environmental factors of aging. Therefore, aging fits the ICD-11 criteria and can be considered a disease. This proposal was submitted to the ICD-11 Joint Task force, and this led to the inclusion of the extension code for "Ageing-related" (XT9T) into the "Causality" section of the ICD-11. These findings might lead to greater focus on biological aging in global health policy and might provide for more opportunities for the new therapy developers.

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HEALTHY LIFE EXTENSION SOCIETY

J Intern Med. 2020 Apr;287(4):373-394. doi: 10.1111/joim.13024. Epub 2020 Feb 27.

A roadmap to build a phenotypic metric of ageing: insights from the Baltimore Longitudinal Study of Aging.

Kuo PL[1,2], Schrack JA[1,2], Shardell MD[1], Levine M[3], Moore AZ[1], An Y[4], Elango P[1], Karikkineth A[5], Tanaka T[1], de Cabo R[1], Zukley LM[5], AlGhatrif M[1,6], Chia CW[7], Simonsick EM[1], Egan JM[7], Resnick SM[4], Ferrucci L[1].

⊕ Author information

Abstract

Over the past three decades, considerable effort has been dedicated to quantifying the pace of ageing yet identifying the most essential metrics of ageing remains challenging due to lack of comprehensive measurements and heterogeneity of the ageing processes. Most of the previously proposed metrics of ageing have been emerged from cross-sectional associations with chronological age and predictive accuracy of mortality, thus lacking a conceptual model of functional or phenotypic domains. Further, such models may be biased by selective attrition and are unable to address underlying biological constructs contributing to functional markers of age-related decline. Using longitudinal data from the Baltimore Longitudinal Study of Aging (BLSA), we propose a conceptual framework to identify metrics of ageing that may capture the hierarchical and temporal relationships between functional ageing, phenotypic ageing and biological ageing based on four hypothesized domains: body composition, energy regulation, homeostatic mechanisms and neurodegeneration/neuroplasticity. We explored the longitudinal trajectories of key variables within these phenotypes using linear mixed-effects models and more than 10 years of data. Understanding the longitudinal trajectories across these domains in the BLSA provides a reference for researchers, informs future refinement of the phenotypic ageing framework and establishes a solid foundation for future models of biological ageing.

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Sarcopenia Definition: The Position Statements of the Sarcopenia Definition and Outcomes Consortium

Objectives: To develop an evidence-based definition of sarcopenia that can facilitate identification of older adults at risk for clinically relevant outcomes (eg, self-reported mobility limitation, falls, fractures, and mortality), the Sarcopenia Definition and Outcomes Consortium (SDOC) crafted a set of position statements informed by a literature review and SDOC's analyses of eight epidemiologic studies, six randomized clinical trials, four cohort studies of special populations, and two nationally representative population-based studies.

Methods: Thirteen position statements related to the putative components of a sarcopenia definition, informed by the SDOC analyses and literature synthesis, were reviewed by an independent international expert panel (panel) iteratively and voted on by the panel during the Sarcopenia Position Statement Conference. Four position statements related to grip strength, three to lean mass derived from dual-energy x-ray absorptiometry (DXA), and four to gait speed; two were summary statements.

Results: The SDOC analyses identified grip strength, either absolute or scaled to measures of body size, as an important discriminator of slowness. Both low grip strength and low usual gait speed independently predicted falls, self-reported mobility limitation, hip fractures, and mortality in community-dwelling older adults. Lean mass measured by DXA was not associated with incident adverse health-related outcomes in community-dwelling older adults with or without adjustment for body size.

Conclusion: The panel agreed that both weakness defined by low grip strength and slowness defined by low usual gait speed should be included in the definition of sarcopenia. These position statements offer a rational basis for an evidence-based definition of sarcopenia. The analyses that informed these position statements are summarized in this article and discussed in accompanying articles in this issue of the journal.

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Discovery, Development, and Future Application of Senolytics: Theories and Predictions

Erin O Wissler Gerdes [1], Yi Zhu [1], Tamar Tchkonia [1], James L Kirkland [1]

Affiliations + expand

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Abstract

Senescent cells accumulate with aging and at etiological sites of multiple diseases, including those accounting for most morbidity, mortality, and health costs. Senescent cells do not replicate, can release factors that cause tissue dysfunction, and yet remain viable. The discovery of senolytic drugs, agents that selectively eliminate senescent cells, created a new route for alleviating age-related dysfunction and diseases. As anticipated for agents targeting fundamental aging mechanisms that are 'root cause' contributors to multiple disorders, potential applications of senolytics are protean. We review the discovery of senolytics, strategies for translation into clinical application, and promising early signals from clinical trials.

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Redox signalling and ageing: insights from *Drosophila*

Claudia Lennicke; Helena M. Cochemé

Ageing and age-related diseases are major challenges for the social, economic and healthcare systems of our society. Amongst many theories, reactive oxygen species (ROS) have been implicated as a driver of the ageing process. As by-products of aerobic metabolism, ROS are able to randomly oxidise macromolecules, causing intracellular damage that accumulates over time and ultimately leads to dysfunction and cell death. However, the genetic overexpression of enzymes involved in the detoxification of ROS or treatment with antioxidants did not generally extend lifespan, prompting a re-evaluation of the causal role for ROS in ageing. More recently, ROS have emerged as key players in normal cellular signalling by oxidising redox-sensitive cysteine residues within proteins. Therefore, while high levels of ROS may be harmful and induce oxidative stress, low levels of ROS may actually be beneficial as mediators of redox signalling. In this context, enhancing ROS production in model organisms can extend lifespan, with biological effects dependent on the site, levels, and specific species of ROS. In this review, we examine the role of ROS in ageing, with a particular focus on the importance of the fruit fly *Drosophila* as a powerful model system to study redox processes *in vivo*.

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Catastrophic Endgames: Emerging Mechanisms of Telomere-Driven Genomic Instability

When cells progress to malignancy, they must overcome a final telomere-mediated proliferative lifespan barrier called replicative crisis. Crisis is characterized by extensive telomere fusion that drives widespread genomic instability, mitotic arrest, hyperactivation of autophagy, and cell death. Recently, it has become apparent that that the resolution of dicentric chromosomes, which arise from telomere fusions during crisis, can initiate a sequence of events that leads to chromothripsis, a form of extreme genomic catastrophe. Chromothripsis is characterized by localized genomic regions containing tens to thousands of rearrangements and it is becoming increasingly apparent that chromothripsis occurs widely across tumor types and has a clinical impact. Here we discuss how telomere dysfunction can initiate genomic complexity and the emerging mechanisms of chromothripsis.

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Curr Opin Genet Dev. 2020 Mar 7;60:48-55. doi: 10.1016/j.gde.2020.02.002. [Epub ahead of print]

The enigma of excessively long telomeres in cancer: lessons learned from rare human POT1 variants.

Gong Y[1], Stock AJ[2], Liu Y[3].

⊕ Author information

Abstract

The discovery that rare POT1 variants are associated with extremely long telomeres and increased cancer predisposition has provided a framework to revisit the relationship between telomere length and cancer development. Telomere shortening is linked with increased risk for cancer. However, over the past decade, there is increasing evidence to show that extremely long telomeres caused by mutations in shelterin components (POT1, TPP1, and RAP1) also display an increased risk of cancer. Here, we will review current knowledge on germline mutations of POT1 identified from cancer-prone families. In particular, we will discuss some common features presented by the mutations through structure-function studies. We will further provide an overview of how POT1 mutations affect telomere length regulation and tumorigenesis.

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Clonal Hematopoiesis: A New Step Linking Inflammation to Heart Failure

Yoshimitsu Yura, Soichi Sano and Kenneth Walsh

Heart failure is a common disease with poor prognosis that is associated with cardiac immune cell infiltration and dysregulated cytokine expression. Recently, the clonal expansion of hematopoietic cells with acquired (i.e., nonheritable) DNA mutations, a process referred to as clonal hematopoiesis, has been reported to be associated with cardiovascular diseases including heart failure. Mechanistic studies have shown that leukocytes that harbor these somatic mutations display altered inflammatory characteristics that worsen the phenotypes associated with heart failure in experimental models. In this review, we summarize recent epidemiological and experimental evidence that support the hypothesis that clonal hematopoiesis-mediated immune cell dysfunction contributes to heart failure and cardiovascular disease in general.

Cells. 2020 Mar 24;9(3). pii: E787. doi: 10.3390/cells9030787.

The FOXO's Advantages of Being a Family: Considerations on Function and Evolution.

Schmitt-Ney M[1].

⊕ Author information

Abstract

The nematode *Caenorhabditis elegans* possesses a unique (with various isoforms) FOXO transcription factor DAF-16, which is notorious for its role in aging and its regulation by the insulin-PI3K-AKT pathway. In humans, five genes (including a protein-coding pseudogene) encode for FOXO transcription factors that are targeted by the PI3K-AKT axis, such as in *C. elegans*. This common regulation and highly conserved DNA-binding domain are the pillars of this family. In this review, I will discuss the possible meaning of possessing a group of very similar proteins and how it can generate additional functionality to more complex organisms. I frame this discussion in relation to the much larger super family of Forkhead proteins to which they belong. FOXO members are very often co-expressed in the same cell type. The overlap of function and expression creates a certain redundancy that might be a safeguard against the accidental loss of FOXO function, which could otherwise lead to disease, particularly, cancer. This is one of the points that will be examined in this "family affair" report.

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HEALTHY LIFE EXTENSION SOCIETY

Aging Cell. 2020 Mar 14:e13136. doi: 10.1111/acel.13136. [Epub ahead of print]

The involvement of stress granules in aging and aging-associated diseases.

Cao X[1], Jin X[1], Liu B[1,2,3].

⊕ Author information

Abstract

Stress granules (SGs) are nonmembrane assemblies formed in cells in response to stress conditions. SGs mainly contain untranslated mRNA and a variety of proteins. RNAs and scaffold proteins with intrinsically disordered regions or RNA-binding domains are essential for the assembly of SGs, and multivalent macromolecular interactions among these components are thought to be the driving forces for SG assembly. The SG assembly process includes regulation through post-translational modification and involvement of the cytoskeletal system. During aging, many intracellular bioprocesses become disrupted by factors such as cellular environmental changes, mitochondrial dysfunction, and decline in the protein quality control system. Such changes could lead to the formation of aberrant SGs, as well as alterations in their maintenance, disassembly, and clearance. These aberrant SGs might in turn promote aging and aging-associated diseases. In this paper, we first review the latest progress on the molecular mechanisms underlying SG assembly and SG functioning under stress conditions. Then, we provide a detailed discussion of the relevance of SGs to aging and aging-associated diseases.

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Probing Pedomorphy and Prolonged Lifespan in Naked Mole-Rats and Dwarf Mice

Pedomorphy, maintenance of juvenile traits throughout life, is most pronounced in extraordinarily long-lived naked mole-rats. Many of these traits (e.g., slow growth rates, low hormone levels, and delayed sexual maturity) are shared with spontaneously mutated, long-lived dwarf mice. Although some youthful traits likely evolved as adaptations to subterranean habitats (e.g., thermolability), the nature of these intrinsic pedomorphic features may also contribute to their prolonged youthfulness, longevity, and healthspan.

OTHER RESEARCH & REVIEWS

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An atlas of human metabolism

Abstract

Genome-scale metabolic models (GEMs) are valuable tools to study metabolism and provide a scaffold for the integrative analysis of omics data. Researchers have developed increasingly comprehensive human GEMs, but the disconnect among different model sources and versions impedes further progress. We therefore integrated and extensively curated the most recent human metabolic models to construct a consensus GEM, Human1. We demonstrated the versatility of Human1 through the generation and analysis of cell- and tissue-specific models using transcriptomic, proteomic, and kinetic data. We also present an accompanying web portal, Metabolic Atlas (**https://www.metabolicatlas.org/**), which facilitates further exploration and visualization of Human1 content. Human1 was created using a version-controlled, open-source model development framework to enable community-driven curation and refinement. This framework allows Human1 to be an evolving shared resource for future studies of human health and disease.

Drug compound screening in single and integrated multi-organoid body-on-a-chip systems

Current practices in drug development have led to therapeutic compounds being approved for widespread use in humans, only to be later withdrawn due to unanticipated toxicity. These occurrences are largely the result of erroneous data generated by *in vivo* and *in vitro* preclinical models that do not accurately recapitulate human physiology. Herein, a human primary cell- and stem cell-derived 3D organoid technology is employed to screen a panel of drugs that were recalled from market by the FDA. The platform is comprised of multiple tissue organoid types that remain viable for at least 28 days, *in vitro*. For many of these compounds, the 3D organoid system was able to demonstrate toxicity. Furthermore, organoids exposed to non-toxic compounds remained viable at clinically relevant doses. Additional experiments were performed on integrated multi-organoid systems containing liver, cardiac, lung, vascular, testis, colon, and brain. These integrated systems proved to maintain viability and expressed functional biomarkers, long-term. Examples are provided that demonstrate how multi-organoid 'body-on-a-chip' systems may be used to model the interdependent metabolism and downstream effects of drugs across multiple tissues in a single platform. Such 3D *in vitro* systems represent a more physiologically relevant model for drug screening and will likely reduce the cost and failure rate associated with the approval of new drugs.

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An open-source drug discovery platform enables ultra-large virtual screens

On average, an approved drug today costs $2-3 billion and takes over ten years to develop[1]. In part, this is due to expensive and time-consuming wet-lab experiments, poor initial hit compounds, and the high attrition rates in the (pre-)clinical phases. Structure-based virtual screening (SBVS) has the potential to mitigate these problems. With SBVS, the quality of the hits improves with the number of compounds screened[2]. However, despite the fact that large compound databases exist, the ability to carry out large-scale SBVSs on computer clusters in an accessible, efficient, and flexible manner has remained elusive. Here we designed VirtualFlow, a highly automated and versatile open-source platform with perfect scaling behaviour that is able to prepare and efficiently screen ultra-large ligand libraries of compounds. VirtualFlow is able to use a variety of the most powerful docking programs. Using VirtualFlow, we have prepared the largest and freely available ready-to-dock ligand library available, with over 1.4 billion commercially available molecules. To demonstrate the power of VirtualFlow, we screened over 1 billion compounds and discovered a small molecule inhibitor (iKeap1) that engages KEAP1 with nanomolar affinity (K_i = 114 nM) and disrupts the interaction between KEAP1 and the transcription factor NRF2. We also identified a set of structurally diverse molecules that bind to KEAP1 with submicromolar affinity. This illustrates the potential of VirtualFlow to access vast regions of the chemical space and identify binders with high affinity for target proteins.

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TEX264 coordinates p97- and SPRTN-mediated resolution of topoisomerase 1-DNA adducts

Eukaryotic topoisomerase 1 (TOP1) regulates DNA topology to ensure efficient DNA replication and transcription. TOP1 is also a major driver of endogenous genome instability, particularly when its catalytic intermediate—a covalent TOP1-DNA adduct known as a TOP1 cleavage complex (TOP1cc)—is stabilised. TOP1ccs are highly cytotoxic and a failure to resolve them underlies the pathology of neurological disorders but is also exploited in cancer therapy where TOP1ccs are the target of widely used frontline anti-cancer drugs. A critical enzyme for TOP1cc resolution is the tyrosyl-DNA phosphodiesterase (TDP1), which hydrolyses the bond that links a tyrosine in the active site of TOP1 to a 3' phosphate group on a single-stranded (ss)DNA break. However, TDP1 can only process small peptide fragments from ssDNA ends, raising the question of how the ~90 kDa TOP1 protein is processed upstream of TDP1. Here we find that TEX264 fulfils this role by forming a complex with the p97 ATPase and the SPRTN metalloprotease. We show that TEX264 recognises both unmodified and SUMO1-modifed TOP1 and initiates TOP1cc repair by recruiting p97 and SPRTN. TEX264 localises to the nuclear periphery, associates with DNA replication forks, and counteracts TOP1ccs during DNA replication. Altogether, our study elucidates the existence of a specialised repair complex required for upstream proteolysis of TOP1ccs and their subsequent resolution.