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Scientific News
1st of September 2019
Sven Bulterijs

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Aging, Drug Discovery & Artificial Intelligence

Date

Tuesday & Thursday, 10-12 September 2019

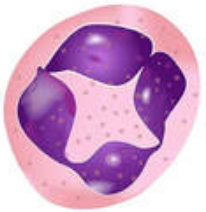
Chairs

Alex Zhavoronkov (InSilico Medicine, Baltimore, United States)
Morten Scheibye-Knudsen (Danish Center for Aging Research/National Institute on Aging, Copenhagen, Denmark)

Abstract

In this symposium, leaders in the aging, longevity, and drug discovery field will describe the latest progress in the molecular, cellular and organismal basis of aging and the search for interventions. Furthermore, the forum will include opinion leaders in AI to discuss the latest advances of this technology in the biopharmaceutical sector and how this can be applied to interventions. This event intends to bridge academic and commercial research and foster collaborations that will result in practical solutions to one of humanity's most challenging problems: aging. A panel of thought-leaders will give us their cutting edge reports on the latest progress in our quest to extend the healthy lifespan of everyone on the planet. Please join us in this merger of driven scientists and global visionaries in an event that may shape the field in years to come.

Kizoo supports LIfT BioSciences



LIfT BioSciences
INNATELY CURING CANCER

LIfT Biosciences is developing the world's first cell therapy to destroy all solid tumours, irrespective of strain or mutation by building the World's 1st cell bank of innately cancer killing neutrophils (a type of white blood cell).

The cell bank will enable LIfT to provide a range of potentially life-saving immuno-oncology cell therapies for different solid tumour types. The first step is to show remission in high unmet need solid tumours by 2021, including Pancreatic Cancer.

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August 9, 2019

Longevity Vision Fund Announces Series B Investment into Exo Imaging

Longevity Vision Fund, a $100M life extension-focused fund founded by longevity investor and visionary Sergey Young announced the completion of a Series B investment round into Exo Imaging.

This brings Exo Imaging's latest fundraising total to nearly $50 million since its launch in 2015. Along Longevity Vision Fund, investments were also made by Applied Ventures, Bold Capital, Creative Ventures, Intel Capital, Magnetar Capital, Nautilus Venture Partners, OSF Healthcare, Rising Tide Fund, Sony Innovation Fund and Wanxiang Healthcare Investments.

Co-founded by Sandeep Akkaraju, Exo Imaging is a California-based medical imaging startup that develops ultrasound systems with the goal of providing physicians a single, handheld probe that can be used for the entire body—from observing the heart and other organs to imaging a person's vasculature or skeletal features in 3D.

"Longevity Vision Fund is excited to have made another step in its mission for affordable and accessible longevity by supporting Exo Imaging in developing portable and inexpensive ultrasound device solutions. We have every faith Exo Imaging will be successful in disrupting the current ultrasound imaging market" said Sergey Young, Founder of Longevity Vision Fund.

Exo Imaging Co-founder and CEO Sandeep Akkaraju said the Series B financing will be used to advance the company's FDA 510(k) clearance process into commercialization and to build its team of engineering, sales and operations professionals.

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A defined human aging phenome

Søren Norge Andreassen [1, *], Michael Ben Ezra [1, *], Morten Scheibye-Knudsen [1]

Aging is among the most complex phenotypes that occur in humans. Identifying the interplay between different age-associated features is undoubtedly critical to our understanding of aging and thus age-associated diseases. Nevertheless, what constitutes human aging is not well characterized. Towards this end, we mined millions of PubMed abstracts for age-associated terms, enabling us to generate a detailed description of the human aging phenotype. We discovered age-associated features in clusters that can be broadly associated with previously defined hallmarks of aging, consequently identifying areas where interventions could be pursued. Importantly, we validated the newly discovered features by manually verifying the prevalence of these features in combined cohorts describing 76 million individuals, allowing us to stratify features in aging that appear to be the most prominent. In conclusion, we propose a comprehensive landscape of human aging: the human aging phenome.

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A metabolic profile of all-cause mortality risk identified in an observational study of 44,168 individuals

Predicting longer-term mortality risk requires collection of clinical data, which is often cumbersome. Therefore, we use a well-standardized metabolomics platform to identify metabolic predictors of long-term mortality in the circulation of 44,168 individuals (age at baseline 18–109), of whom 5512 died during follow-up. We apply a stepwise (forward-backward) procedure based on meta-analysis results and identify 14 circulating biomarkers independently associating with all-cause mortality. Overall, these associations are similar in men and women and across different age strata. We subsequently show that the prediction accuracy of 5- and 10-year mortality based on a model containing the identified biomarkers and sex (C-statistic = 0.837 and 0.830, respectively) is better than that of a model containing conventional risk factors for mortality (C-statistic = 0.772 and 0.790, respectively). The use of the identified metabolic profile as a predictor of mortality or surrogate endpoint in clinical studies needs further investigation.

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Identification and Application of Gene Expression Signatures Associated with Lifespan Extension

Several pharmacological, dietary, and genetic interventions that increase mammalian lifespan are known, but general principles of lifespan extension remain unclear. Here, we performed RNA sequencing (RNA-seq) analyses of mice subjected to 8 longevity interventions. We discovered a feminizing effect associated with growth hormone regulation and diminution of sex-related differences. Expanding this analysis to 17 interventions with public data, we observed that many interventions induced similar gene expression changes. We identified hepatic gene signatures associated with lifespan extension across interventions, including upregulation of oxidative phosphorylation and drug metabolism, and showed that perturbed pathways may be shared across tissues. We further applied the discovered longevity signatures to identify new lifespan-extending candidates, such as chronic hypoxia, KU-0063794, and ascorbyl-palmitate. Finally, we developed GENtervention, an app that visualizes associations between gene expression changes and longevity. Overall, this study describes general and specific transcriptomic programs of lifespan extension in mice and provides tools to discover new interventions.

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Improved precision of epigenetic clock estimates across tissues and its implication for biological ageing

Background

DNA methylation changes with age. Chronological age predictors built from DNA methylation are termed 'epigenetic clocks'. The deviation of predicted age from the actual age ('age acceleration residual', AAR) has been reported to be associated with death. However, it is currently unclear how a better prediction of chronological age affects such association.

Methods

In this study, we build multiple predictors based on training DNA methylation samples selected from 13,661 samples (13,402 from blood and 259 from saliva). We use the Lothian Birth Cohorts of 1921 (LBC1921) and 1936 (LBC1936) to examine whether the association between AAR (from these predictors) and death is affected by (1) improving prediction accuracy of an age predictor as its training sample size increases (from 335 to 12,710) and (2) additionally correcting for confounders (i.e., cellular compositions). In addition, we investigated the performance of our predictor in non-blood tissues.

Results

We found that in principle, a near-perfect age predictor could be developed when the training sample size is sufficiently large. The association between AAR and mortality attenuates as prediction accuracy increases. AAR from our best predictor (based on Elastic Net, https://github.com/qzhang314/DNAm-based-age-predictor) exhibits no association with mortality in both LBC1921 (hazard ratio = 1.08, 95% CI 0.91–1.27) and LBC1936 (hazard ratio = 1.00, 95% CI 0.79–1.28). Predictors based on small sample size are prone to confounding by cellular compositions relative to those from large sample size. We observed comparable performance of our predictor in non-blood tissues with a multi-tissue-based predictor.

Conclusions

This study indicates that the epigenetic clock can be improved by increasing the training sample size and that its association with mortality attenuates with increased prediction of chronological age.

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Supercentenarians and the oldest-old are concentrated into regions with no birth certificates and short lifespans

Saul Justin Newman

doi: https://doi.org/10.1101/704080

This article is a preprint and has not been peer-reviewed [what does this mean?].

Abstract

The observation of individuals attaining remarkable ages, and their concentration into geographic sub-regions or 'blue zones', has generated considerable scientific interest. Proposed drivers of remarkable longevity include high vegetable intake, strong social connections, and genetic markers. Here, we reveal new predictors of remarkable longevity and 'supercentenarian' status. In the United States, supercentenarian status is predicted by the absence of vital registration. The state-specific introduction of birth certificates is associated with a 69-82% fall in the number of supercentenarian records. In Italy, which has more uniform vital registration, remarkable longevity is instead predicted by low per capita incomes and a short life expectancy. Finally, the designated 'blue zones' of Sardinia, Okinawa, and Ikaria corresponded to regions with low incomes, low literacy, high crime rate and short life expectancy relative to their national average. As such, relative poverty and short lifespan constitute unexpected predictors of centenarian and supercentenarian status, and support a primary role of fraud and error in generating remarkable human age records.

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Aging (Albany NY). 2019 Aug 26;11. doi: 10.18632/aging.102200. [Epub ahead of print]

Identification and validation of four hub genes involved in the plaque deterioration of atherosclerosis.

Chen P[1], Chen Y[2], Wu W[1], Chen L[1], Yang X[1], Zhang S[1].

Author information

Abstract

In recent years, intense research has been conducted to explore the diagnostic value of mRNA expression differences in atherosclerosis (AS). Nevertheless, because various technology platforms are applied and sample sizes are small, the results are inconsistent among the studies. We conducted a comprehensive analysis of a total of 161 tissue samples from 4 published studies after evaluating 230 datasets from the Gene Expression Omnibus and ArrayExpress. Adopting the newly published robust rank aggregation approach, combined with Kyoto Encyclopedia of Genes and Genomes pathway analysis, Gene Ontology functional enrichment analysis, and protein-protein interaction network construction, we identified four significantly upregulated genes (*CCL4*, *CCL18*, *MMP9* and *SPP1*) for diagnosing AS, even in the advanced stage. Then, we performed gene set enrichment analysis to identify the pathways that were most affected by altered mRNA expression in atherosclerotic plaques. We found that four hub genes cooperatively targeted lipid metabolism and inflammatory immune-related pathways and validated their high expression levels in ruptured plaques by qRT-PCR, western blot analysis and immunohistochemical staining. In summary, our study showed that these genes can be used as interventional targets for plaque progression, and the results suggested we should focus on small changes in these key indicators in the clinical setting.

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Proc Natl Acad Sci U S A. 2019 Aug 27;116(35):17383-17392. doi: 10.1073/pnas.1900055116. Epub 2019 Aug 14.

Dietary restriction improves proteostasis and increases life span through endoplasmic reticulum hormesis.

Matai L[1,2,3], Sarkar GC[1], Chamoli M[1], Malik Y[1], Kumar SS[4], Rautela U[1], Jana NR[4], Chakraborty K[2,3], Mukhopadhyay A[5].

Author information

Abstract

Unfolded protein response (UPR) of the endoplasmic reticulum (UPR^{ER}) helps maintain proteostasis in the cell. The ability to mount an effective UPR^{ER} to external stress ($iUPR^{ER}$) decreases with age and is linked to the pathophysiology of multiple age-related disorders. Here, we show that a transient pharmacological ER stress, imposed early in development on *Caenorhabditis elegans*, enhances proteostasis, prevents $iUPR^{ER}$ decline with age, and increases adult life span. Importantly, dietary restriction (DR), that has a conserved positive effect on life span, employs this mechanism of ER hormesis for longevity assurance. We found that only the IRE-1-XBP-1 branch of UPR^{ER} is required for the longevity effects, resulting in increased ER-associated degradation (ERAD) gene expression and degradation of ER resident proteins during DR. Further, both ER hormesis and DR protect against polyglutamine aggregation in an IRE-1-dependent manner. We show that the DR-specific FOXA transcription factor PHA-4 transcriptionally regulates the genes required for ER homeostasis and is required for ER preconditioning-induced life span extension. Finally, we show that ER hormesis improves proteostasis and viability in a mammalian cellular model of neurodegenerative disease. Together, our study identifies a mechanism by which DR offers its benefits and opens the possibility of using ER-targeted pharmacological interventions to mimic the prolongevity effects of DR.

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Alternate Day Fasting Improves Physiological and Molecular Markers of Aging in Healthy, Non-obese Humans

Caloric restriction and intermittent fasting are known to prolong life- and healthspan in model organisms, while their effects on humans are less well studied. In a randomized controlled trial study (ClinicalTrials.gov identifier: NCT02673515), we show that 4 weeks of strict alternate day fasting (ADF) improved markers of general health in healthy, middle-aged humans while causing a 37% calorie reduction on average. No adverse effects occurred even after >6 months. ADF improved cardiovascular markers, reduced fat mass (particularly the trunk fat), improving the fat-to-lean ratio, and increased β-hydroxybutyrate, even on non-fasting days. On fasting days, the pro-aging amino-acid methionine, among others, was periodically depleted, while polyunsaturated fatty acids were elevated. We found reduced levels sICAM-1 (an age-associated inflammatory marker), low-density lipoprotein, and the metabolic regulator triiodothyronine after long-term ADF. These results shed light on the physiological impact of ADF and supports its safety. ADF could eventually become a clinically relevant intervention.

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Radiat Res. 2019 Aug 7. doi: 10.1667/RR15385.1. [Epub ahead of print]

Life-Shortening Effect of Chronic Low-Dose-Rate Irradiation in Calorie-Restricted Mice.

Yamauchi K[1], Ono T[1], Ayabe Y[2], Hisamatsu S[2], Yoneya M[1], Tsutsumi Y[3], Komura JI[1].

Author information

Abstract

Calorie restriction is known to influence several physiological processes and to alleviate the late effects of radiation exposure such as neoplasm induction and life shortening. However, earlier related studies were limited to acute radiation exposure. Therefore, in this study we examined the influence of chronic low-dose-rate irradiation on lifespan. Young male B6C3F1/Jcl mice were divided randomly into two groups, which were fed either a low-calorie (65 kcal/week) or high-calorie (95 kcal/week) diet. The latter is comparable to *ad libitum* feeding. The animals in the irradiated group were continuously exposed to gamma rays for 400 days at 20 mGy/day, resulting in a total dose of 8 Gy. Exposure and calorie restriction were initiated at 8 weeks of age and the diets were maintained for life. The life-shortening effects from chronic whole-body irradiation were compared between the groups. Body weights were reduced in calorie-restricted mice irrespective of radiation treatment. Radiation induced a shortened median lifespan in both groups, but to a greater extent in the calorie-restricted mice. These results suggest that calorie restriction may sensitize mice to chronic low-dose-rate radiation exposure to produce a life-shortening effect rather than alleviating the effects of radiation.

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A nutritional memory impairs survival, transcriptional and metabolic response to dietary restriction in old mice

Oliver Hahn, Lisa F. Drews, An Nguyen, Takashi Tatsuta, Lisonia Gkioni, Oliver Hendrich, Qifeng Zhang, Thomas Langer, Scott Pletcher, Michael J. O. Wakelam, Andreas Beyer, Sebastian Grönke, Linda Partridge

doi: https://doi.org/10.1101/730853

Abstract

Dietary restriction (DR) during adulthood can greatly extend lifespan and improve metabolic health in diverse species. However, whether DR in mammals is still effective when applied for the first time at old age remains elusive. Here, we conducted a late-life DR switch experiment employing 800 mice, by switching old animals from ad libitum (AL) to DR and vice versa. Strikingly, the switch from DR-to-AL acutely increased mortality, while the switch from AL-to-DR caused only a weak and gradual increase in survival, highlighting a memory of earlier nutrition. A significant association between fat preservation and survival response pointed to the white adipose tissue (WAT) as a potential memory source. Consistently, post-switch RNA-seq profiling in liver and WAT demonstrated that the transcriptional and metabolic program of chronic DR remained largely refractory to the AL-to-DR switch specifically in adipose tissue. Integration of lipidomics confirmed impaired membrane lipogenesis and limited mitochondrial copy number increase under late-life DR as functional consequences of this memory effect. Together, our results provide evidence for a nutritional memory as a limiting factor for DR-induced longevity and metabolic remodeling of WAT in mammals.

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Chemoptogenetic damage to mitochondria causes rapid telomere dysfunction

Wei Qian, Namrata Kumar, Vera Roginskaya, Elise Fouquerel, Patricia L. Opresko, Sruti Shiva, Simon C. Watkins, Dmytro Kolodieznyi, Marcel P. Bruchez, and Bennett Van Houten

Reactive oxygen species (ROS) play important roles in aging, inflammation, and cancer. Mitochondria are an important source of ROS; however, the spatiotemporal ROS events underlying oxidative cellular damage from dysfunctional mitochondria remain unresolved. To this end, we have developed and validated a chemoptogenetic approach that uses a mitochondrially targeted fluorogen-activating peptide (Mito-FAP) to deliver a photosensitizer MG-2I dye exclusively to this organelle. Light-mediated activation (660 nm) of the Mito-FAP–MG-2I complex led to a rapid loss of mitochondrial respiration, decreased electron transport chain complex activity, and mitochondrial fragmentation. Importantly, one round of singlet oxygen produced a persistent secondary wave of mitochondrial superoxide and hydrogen peroxide lasting for over 48 h after the initial insult. By following ROS intermediates, we were able to detect hydrogen peroxide in the nucleus through ratiometric analysis of the oxidation of nuclear cysteine residues. Despite mitochondrial DNA (mtDNA) damage and nuclear oxidative stress induced by dysfunctional mitochondria, there was a lack of gross nuclear DNA strand breaks and apoptosis. Targeted telomere analysis revealed fragile telomeres and telomere loss as well as 53BP1-positive telomere dysfunction-induced foci (TIFs), indicating that DNA double-strand breaks occurred exclusively in telomeres as a direct consequence of mitochondrial dysfunction. These telomere defects activated ataxia-telangiectasia mutated (ATM)-mediated DNA damage repair signaling. Furthermore, ATM inhibition exacerbated the Mito-FAP–induced mitochondrial dysfunction and sensitized cells to apoptotic cell death. This profound sensitivity of telomeres through hydrogen peroxide induced by dysregulated mitochondria reveals a crucial mechanism of telomere–mitochondria communication underlying the pathophysiological role of mitochondrial ROS in human diseases.

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Niche stiffness underlies the ageing of central nervous system progenitor cells

Ageing causes a decline in tissue regeneration owing to a loss of function of adult stem cell and progenitor cell populations[1]. One example is the deterioration of the regenerative capacity of the widespread and abundant population of central nervous system (CNS) multipotent stem cells known as oligodendrocyte progenitor cells (OPCs)[2]. A relatively overlooked potential source of this loss of function is the stem cell 'niche'—a set of cell-extrinsic cues that include chemical and mechanical signals[3,4]. Here we show that the OPC microenvironment stiffens with age, and that this mechanical change is sufficient to cause age-related loss of function of OPCs. Using biological and synthetic scaffolds to mimic the stiffness of young brains, we find that isolated aged OPCs cultured on these scaffolds are molecularly and functionally rejuvenated. When we disrupt mechanical signalling, the proliferation and differentiation rates of OPCs are increased. We identify the mechanoresponsive ion channel PIEZO1 as a key mediator of OPC mechanical signalling. Inhibiting PIEZO1 overrides mechanical signals in vivo and allows OPCs to maintain activity in the ageing CNS. We also show that PIEZO1 is important in regulating cell number during CNS development. Thus we show that tissue stiffness is a crucial regulator of ageing in OPCs, and provide insights into how the function of adult stem and progenitor cells changes with age. Our findings could be important not only for the development of regenerative therapies, but also for understanding the ageing process itself.

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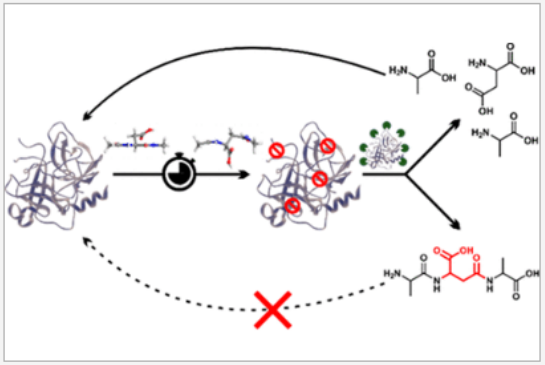
Spontaneous Isomerization of Long-Lived Proteins Provides a Molecular Mechanism for the Lysosomal Failure Observed in Alzheimer's Disease

Tyler R. Lambeth, Dylan L. Riggs, Lance E. Talbert, Jin Tang, Emily Coburn, Amrik S. Kang, Jessica Noll, Catherine Augello, Byron D. Ford and Ryan R. Julian*

Proteinaceous aggregation is a well-known observable in Alzheimer's disease (AD), but failure and storage of lysosomal bodies within neurons is equally ubiquitous and actually precedes bulk accumulation of extracellular amyloid plaque. In fact, AD shares many similarities with certain lysosomal storage disorders though establishing a biochemical connection has proven difficult. Herein, we demonstrate that isomerization and epimerization, which are spontaneous chemical modifications that occur in long-lived proteins, prevent digestion by the proteases in the lysosome (namely, the cathepsins). For example, isomerization of aspartic acid into l-isoAsp prevents digestion of the N-terminal portion of Aβ by cathepsin L, one of the most aggressive lysosomal proteases. Similar results were obtained after examination of various target peptides with a full series of cathepsins, including endo-, amino-, and carboxy-peptidases. In all cases peptide fragments too long for transporter recognition or release from the lysosome persisted after treatment, providing a mechanism for eventual lysosomal storage and bridging the gap between AD and lysosomal storage disorders. Additional experiments with microglial cells confirmed that isomerization disrupts proteolysis in active lysosomes. These results are easily rationalized in terms of protease active sites, which are engineered to precisely orient the peptide backbone and cannot accommodate the backbone shift caused by isoaspartic acid or side chain dislocation resulting from epimerization. Although Aβ is known to be isomerized and epimerized in plaques present in AD brains, we further establish that the rates of modification for aspartic acid in positions 1 and 7 are fast and could accrue prior to plaque formation. Spontaneous chemistry can therefore provide modified substrates capable of inducing gradual lysosomal failure, which may play an important role in the cascade of events leading to the disrupted proteostasis, amyloid formation, and tauopathies associated with AD.



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Cyclic O_3 exposure synergizes with aging leading to memory impairment in male APOE ε3, but not APOE ε4, targeted replacement mice

The etiology of late-onset Alzheimer's disease is unknown. Recent epidemiological studies suggest that exposure to high levels of ozone (O_3) may be a risk factor for late-onset Alzheimer's disease. Nonetheless, whether and how O_3 exposure contributes to AD development remains to be determined. In this study, we tested the hypothesis that O_3 exposure synergizes with the genetic risk factor *APOE ε4* and aging leading to AD, using male apolipoprotein E (apoE)4 and apoE3 targeted replacement mice as men have increased risk exposure to high levels of O_3 via working environments and few studies have addressed *APOE ε4* effects on males. Surprisingly, our results show that O_3 exposure impairs memory in old apoE3, but not old apoE4 or young apoE3 and apoE4, male mice. Further studies show that old apoE4 mice have increased hippocampal activities or expression of some enzymes involved in antioxidant defense, diminished protein oxidative modification, and neuroinflammation following O_3 exposure compared with old apoE3 mice. These novel findings highlight the complexity of interactions between *APOE* genotype, age, and environmental exposure in AD development.

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Nicotinamide Riboside Augments the Aged Human Skeletal Muscle NAD^+ Metabolome and Induces Transcriptomic and Anti-inflammatory Signatures

Nicotinamide adenine dinucleotide (NAD^+) is modulated by conditions of metabolic stress and has been reported to decline with aging in preclinical models, but human data are sparse. Nicotinamide riboside (NR) supplementation ameliorates metabolic dysfunction in rodents. We aimed to establish whether oral NR supplementation in aged participants can increase the skeletal muscle NAD^+ metabolome and if it can alter muscle mitochondrial bioenergetics. We supplemented 12 aged men with 1 g NR per day for 21 days in a placebo-controlled, randomized, double-blind, crossover trial. Targeted metabolomics showed that NR elevated the muscle NAD^+ metabolome, evident by increased nicotinic acid adenine dinucleotide and nicotinamide clearance products. Muscle RNA sequencing revealed NR-mediated downregulation of energy metabolism and mitochondria pathways, without altering mitochondrial bioenergetics. NR also depressed levels of circulating inflammatory cytokines. Our data establish that oral NR is available to aged human muscle and identify anti-inflammatory effects of NR.

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Analysis of somatic mutations identifies signs of selection during in vitro aging of primary dermal fibroblasts

Narisu Narisu, Rebecca Rothwell, Peter Vrtačnik, Sofía Rodríguez, John Didion, Sebastian Zöllner, Michael R. Erdos, Francis S. Collins ✉, Maria Eriksson

Somatic mutations are critical for cancer development and may play a role in age-related functional decline. Here, we used deep sequencing to analyze the prevalence of somatic mutations during in vitro cell aging. Primary dermal fibroblasts from healthy subjects of young and advanced age, from Hutchinson–Gilford progeria syndrome and from xeroderma pigmentosum complementation groups A and C, were first restricted in number and then expanded in vitro. DNA was obtained from cells pre- and post-expansion and sequenced at high depth (1656× mean coverage), over a cumulative 290 kb target region, including the exons of 44 aging-related genes. Allele frequencies of 58 somatic mutations differed between the pre- and post-cell culture expansion passages. Mathematical modeling revealed that the frequency change of three of the 58 mutations was unlikely to be explained by genetic drift alone, indicative of positive selection. Two of these three mutations, *CDKN2A* c.53C>T (T18M) and *ERCC8* c.*772T>A, were identified in cells from a patient with XPA. The allele frequency of the *CDKN2A* mutation increased from 0% to 55.3% with increasing cell culture passage. The third mutation, *BRCA2* c.6222C>T (H2074H), was identified in a sample from a healthy individual of advanced age. However, further validation of the three mutations suggests that other unmeasured variants probably provide the selective advantage in these cells. Our results reinforce the notions that somatic mutations occur during aging and that some are under positive selection, supporting the model of increased tissue heterogeneity with increased age.

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Stabilizing heterochromatin by DGCR8 alleviates senescence and osteoarthritis

DiGeorge syndrome critical region 8 (DGCR8) is a critical component of the canonical microprocessor complex for microRNA biogenesis. However, the non-canonical functions of DGCR8 have not been studied. Here, we demonstrate that DGCR8 plays an important role in maintaining heterochromatin organization and attenuating aging. An N-terminal-truncated version of DGCR8 ($DR8^{dex2}$) accelerated senescence in human mesenchymal stem cells (hMSCs) independent of its microRNA-processing activity. Further studies revealed that DGCR8 maintained heterochromatin organization by interacting with the nuclear envelope protein Lamin B1, and heterochromatin-associated proteins, KAP1 and HP1γ. Overexpression of any of these proteins, including DGCR8, reversed premature senescent phenotypes in $DR8^{dex2}$ hMSCs. Finally, DGCR8 was downregulated in pathologically and naturally aged hMSCs, whereas DGCR8 overexpression alleviated hMSC aging and mouse osteoarthritis. Taken together, these analyses uncovered a novel, microRNA processing-independent role in maintaining heterochromatin organization and attenuating senescence by DGCR8, thus representing a new therapeutic target for alleviating human aging-related disorders.

Protein & Cell

pp 1–6 | Cite as

Low-dose quercetin positively regulates mouse healthspan

Authors | Authors and affiliations

Lingling Geng, Zunpeng Liu, Si Wang, Shuhui Sun, Shuai Ma, Xiaoqian Liu, Piu Chan, Liang Sun, Moshi Song ✉, Weiqi Zhang ✉, Guang-Hui Liu ✉, Jing Qu ✉

Dear Editor,

Aging is the leading risk factor for many chronic diseases, accounting for almost 60% of all deaths worldwide. How to achieve healthy aging, alleviate aging-related diseases, and extend healthspan has become a main topic of biomedical research (He et al., 2019). Geroprotective compounds, such as metformin and rapamycin, have been shown to improve both healthspan and lifespan in mice (Martin-Montalvo et al., 2013; Bitto et al., 2016), whereas nicotinamide partially improves healthspan in mice (Mitchell et al., 2018). In addition, senolytics, compounds that eliminate senescent cells, have been proven to improve physical function and increase lifespan in mice (Xu et al., 2018). Although none have proven to be clinically reliable in delaying aging or treating frailty in humans, these compounds have already provoked enthusiasm for identifying a potential "elixir". Therefore, the exploration of more geroprotective compounds, especially natural active compounds, holds great potential for the development of geriatric medicines.

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The Matrisome during Aging and Longevity: A Systems-Level Approach towards Defining Matreotypes Promoting Healthy Aging

Collin Ewald *

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Abstract

Accumulation of damage is generally considered the cause of aging. Interventions that delay aging mobilize mechanisms that protect and repair cellular components. Consequently, research has been focused on studying the protective and homeostatic mechanisms within cells. However, in humans and other multicellular organisms, cells are surrounded by extracellular matrices (ECM), which are important for tissue structure, function and intercellular communication. During aging, components of the ECM become damaged through fragmentation, glycation, crosslinking, and accumulation of protein aggregation, all of which contribute to age-related pathologies. Interestingly, placing senescent cells into a young ECM rejuvenates them and we found that many longevity-assurances pathways re-activate *de-novo*synthesis of ECM proteins during aging. This raises the question of what constitutes a young ECM to reverse aging or maintain health? In order to make inroads to answering this question, I suggest a systems-level approach of quantifying the matrisome or ECM compositions reflecting health, pathology, or phenotype and propose a novel term, the "matreotype", to describe this. The matreotype is defined as the composition and modification of ECM or matrisome proteins associated with or caused by a phenotype, such as longevity, or a distinct and acute physiological state, as observed during aging or disease. Every cell type produces its unique ECM. Interestingly, cancer-cell types can even be identified based on their unique ECM composition. Thus, the matreotype reflects cellular identity and physiological status. Defined matreotypes could be used as biomarkers or prognostic factors for disease or health status during aging with potential relevance for personalized medicine. Treatment with biologics that alter ECM-to-cell mechanotransduction might be a strategy to reverse age-associated pathologies. An understanding of how to reverse from an old to a young matreotype might point towards novel strategies to rejuvenate cells and help maintain tissue homeostasis to promote health during aging.

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Aging-associated changes in transcriptional elongation influence metazoan longevity

Cédric Debès, Sebastian Grönke, Özlem Karalay, Luke Tain, Shuhei Nakamura, Oliver Hahn, Carina Weigelt, Anne Zirkel, Konstantinos Sofiadis, Lilija Brant, Bernd Wollnik, Torsten Kubacki, Martin Späth, Bernhard Schermer, Thomas Benzing, Roman-Ulrich Müller, Argyris Papantonis, Adam Antebi, Linda Partridge, Andreas Beyer

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Abstract

Aging impairs cellular homeostasis, thereby compromising multiple cellular processes, including transcription and splicing. However, the molecular mechanisms at work, and hence ways of preventing loss of transcriptional fidelity, are so far elusive. We analyzed changes in genome-wide, transcription-coupled processes with age in *Caenorhabditis elegans, Drosophila melanogaster, Mus musculus, Rattus norvegicus* and *Homo sapiens*. Using total RNA profiling, we quantified transcriptional elongation speed (Pol-II speed). Genome-averaged Pol-II speed increased with age in all five species. Lifespan-extending dietary restriction and lowered insulin signaling both rescued these age-related trends. Experimentally reducing Pol-II speed in worms and flies increased lifespan. These findings uncover fundamental molecular mechanisms driving animal aging and underlying lifespan-extending interventions, and point to possible preventative measures.

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Comment on this paper

Stress Resistance Screen in a Human Primary Cell Line Identifies Small Molecules that Affect Aging Pathways and Extend *C. elegans'* Lifespan

Peichuan Zhang, Yuying Zhai, James Cregg, Kenny Kean-Hooi Ang, Michelle Arkin, Cynthia Kenyon

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This article is a preprint and has not been peer-reviewed [what does this mean?].

Abstract

Increased resistance to environmental stress at the cellular level is correlated with the longevity of long-lived mutants and wild-animal species. Moreover, in experimental organisms, screens for increased stress resistance have yielded mutants that are long-lived. To find entry points for small molecules that might extend healthy longevity in humans, we screened ~100,000 small molecules in a human primary-fibroblast cell line and identified a set that increased oxidative-stress resistance. Some of the hits fell into structurally-related chemical groups, suggesting that they may act on common targets. Two small molecules increased *C. elegans'* stress resistance, and at least 9 extended their lifespan by ~10-50%. Thus, screening for increased stress resistance in human cells can enrich for compounds with promising pro-longevity effects. Further characterization of these compounds, including a chalcone that promoted stress resistance independently of *NRF2*, may elucidate new ways to extend healthy human lifespan.

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The longevity-promoting factor, TCER-1, widely represses stress resistance and innate immunity

Stress resistance and longevity are positively correlated but emerging evidence indicates that they are physiologically distinct. Identifying factors with distinctive roles in these processes is challenging because pro-longevity genes often enhance stress resistance. We demonstrate that TCER-1, the *Caenorhabditis elegans* homolog of human transcription elongation and splicing factor, TCERG1, has opposite effects on lifespan and stress resistance. We previously showed that *tcer-1* promotes longevity in germline-less *C. elegans* and reproductive fitness in wild-type animals. Surprisingly, *tcer-1* mutants exhibit exceptional resistance against multiple stressors, including infection by human opportunistic pathogens, whereas, TCER-1 overexpression confers immuno-susceptibility. TCER-1 inhibits immunity only during fertile stages of life. Elevating its levels ameliorates the fertility loss caused by infection, suggesting that TCER-1 represses immunity to augment fecundity. TCER-1 acts through repression of PMK-1 as well as PMK-1-independent factors critical for innate immunity. Our data establish key roles for TCER-1 in coordinating immunity, longevity and fertility, and reveal mechanisms that distinguish length of life from functional aspects of aging.

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Prostaglandin signals from adult germline stem cells delay somatic ageing of *Caenorhabditis elegans*

A moderate reduction in body temperature can induce a remarkable lifespan extension. Here we examine the link between cold temperature, germline fitness and organismal longevity. We show that low temperature reduces age-associated exhaustion of germline stem cells (GSCs) in *Caenorhabditis elegans*, a process modulated by thermosensory neurons. Notably, robust self-renewal of adult GSCs delays reproductive ageing and is required for extended lifespan at cold temperatures (10 °C, 15 °C). These cells release prostaglandin E2 (PGE2) to induce *cbs-1* expression in the intestine, increasing the somatic production of hydrogen sulfide, a gaseous signalling molecule that prolongs lifespan. Loss of adult GSCs reduces intestinal *cbs-1* expression and cold-induced longevity, whereas application of exogenous PGE2 rescues these phenotypes. Importantly, tissue-specific intestinal overexpression of *cbs-1* mimics cold-temperature conditions and extends longevity even at warm temperatures (25 °C). Thus, our results indicate that GSCs communicate with somatic tissues to coordinate extended reproductive capacity with longevity.

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ATGL-1 mediates the effect of dietary restriction and the insulin/IGF-1 signaling pathway on longevity in *C. elegans*

Nava Zaarur, Kathleen Desevin, James Mackenzie, Avery Lord, Alla Grishok, Konstantin V. Kandror

Animal lifespan is controlled through genetic pathways that are conserved from nematodes to humans. Lifespan-promoting conditions in nematodes include fasting and a reduction of insulin/IGF signaling. Here we aimed to investigate the input of the *Caenorhabditis elegans* homologue of the mammalian rate-limiting lipolytic enzyme Adipose Triglyceride Lipase, ATGL-1, in longevity control.

Methods

We used a combination of genetic and biochemical approaches to determine the role of ATGL-1 in accumulation of triglycerides and regulation of longevity.

Results

We found that expression of ATGL is increased in the insulin receptor homologue mutant *daf-2* in a FoxO/DAF-16-dependent manner. ATGL-1 is also up-regulated by fasting and in the *eat-2* loss-of-function mutant strain. Overexpression of ATGL-1 increases basal and maximal oxygen consumption rate and extends lifespan in *C. elegans*. Reduction of ATGL-1 function suppresses longevity of the long-lived mutants *eat-2* and *daf-2*.

Conclusion

Our results demonstrate that ATGL is required for extended lifespan downstream of both dietary restriction and reduced insulin/IGF signaling.

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Neuronal TORC1 modulates longevity via AMPK and cell nonautonomous regulation of mitochondrial dynamics in *C. elegans*.

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Author information

Abstract

Target of rapamycin complex 1 (TORC1) and AMP-activated protein kinase (AMPK) antagonistically modulate metabolism and aging. However, how they coordinate to determine longevity and if they act via separable mechanisms is unclear. Here, we show that neuronal AMPK is essential for lifespan extension from TORC1 inhibition, and that TORC1 suppression increases lifespan cell non autonomously via distinct mechanisms from global AMPK activation. Lifespan extension by null mutations in genes encoding *raga-1* (RagA) or *rsks-1* (S6K) is fully suppressed by neuronal-specific rescues. Loss of RAGA-1 increases lifespan via maintaining mitochondrial fusion. Neuronal RAGA-1 abrogation of *raga-1* mutant longevity requires UNC-64/syntaxin, and promotes mitochondrial fission cell nonautonomously. Finally, deleting the mitochondrial fission factor DRP-1 renders the animal refractory to the pro-aging effects of neuronal RAGA-1. Our results highlight a new role for neuronal TORC1 in cell nonautonomous regulation of longevity, and suggest TORC1 in the central nervous system might be targeted to promote healthy aging.

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Skeletal Muscle mTORC1 Activation Increases Energy Expenditure and Reduces Longevity in Mice

Erin J. Stephenson, JeAnna R. Redd, Detrick Snyder, Quynh T. Tran, Binbin Lu, Matthew J. Peloquin, Molly C. Mulcahy, Innocence Harvey, Kaleigh Fisher, Joan C. Han, Nathan Qi, Alan R. Saltiel, Dave Bridges

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Abstract

The mechanistic target of rapamycin (mTORC1) is a nutrient responsive protein kinase complex that helps co-ordinate anabolic processes across all tissues. There is evidence that signaling through mTORC1 in skeletal muscle may be a determinant of energy expenditure and aging and therefore components downstream of mTORC1 signaling may be potential targets for treating obesity and age-associated metabolic disease. Here, we generated mice with *Ckmm-Cre* driven ablation of *Tsc1*, which confers constitutive activation of mTORC1 in skeletal muscle and performed unbiased transcriptional analyses to identify pathways and candidate genes that may explain how skeletal muscle mTORC1 activity regulates energy balance and aging. Activation of skeletal muscle mTORC1 produced a striking resistance to diet-and age-induced obesity without inducing systemic insulin resistance. We found that increases in energy expenditure following a high fat diet were mTORC1-dependent and that elevated energy expenditure caused by ablation of *Tsc1* coincided with the upregulation of skeletal muscle-specific thermogenic mechanisms that involve sarcolipin-driven futile cycling of Ca^{2+} through SERCA2. Additionally, we report that constitutive activation of mTORC1 in skeletal muscle reduces lifespan. These findings support the hypothesis that activation of mTORC1 and its downstream targets, specifically in skeletal muscle, may play a role in nutrient-dependent thermogenesis and aging.

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Hypothalamic mTORC2 is essential for metabolic health and longevity

The mechanistic target of rapamycin (mTOR) is an evolutionarily conserved protein kinase that regulates growth and metabolism. mTOR is found in two protein complexes, mTORC1 and mTORC2, that have distinct components and substrates and are both inhibited by rapamycin, a macrolide drug that robustly extends lifespan in multiple species including worms and mice. Although the beneficial effect of rapamycin on longevity is generally attributed to reduced mTORC1 signaling, disruption of mTORC2 signaling can also influence the longevity of worms, either positively or negatively depending on the temperature and food source. Here, we show that loss of hypothalamic mTORC2 signaling in mice decreases activity level, increases the set point for adiposity, and renders the animals susceptible to diet-induced obesity. Hypothalamic mTORC2 signaling normally increases with age, and mice lacking this pathway display higher fat mass and impaired glucose homeostasis throughout life, become more frail with age, and have decreased overall survival. We conclude that hypothalamic mTORC2 is essential for the normal metabolic health, fitness, and lifespan of mice. Our results have implications for the use of mTORC2-inhibiting pharmaceuticals in the treatment of brain cancer and diseases of aging.

Longevity is determined by ETS transcription factors in multiple tissues and diverse species

Ageing populations pose one of the main public health crises of our time. Reprogramming gene expression by altering the activities of sequence-specific transcription factors (TFs) can ameliorate deleterious effects of age. Here we explore how a circuit of TFs coordinates pro-longevity transcriptional outcomes, which reveals a multi-tissue and multi-species role for an entire protein family: the E-twenty-six (ETS) TFs. In *Drosophila*, reduced insulin/IGF signalling (IIS) extends lifespan by coordinating activation of *Aop*, an ETS transcriptional repressor, and *Foxo*, a Forkhead transcriptional activator. *Aop* and *Foxo* bind the same genomic loci, and we show that, individually, they effect similar transcriptional programmes *in vivo*. In combination, *Aop* can both moderate or synergise with *Foxo*, dependent on promoter context. Moreover, *Foxo* and *Aop* oppose the gene-regulatory activity of *Pnt*, an ETS transcriptional activator. Directly knocking down *Pnt* recapitulates aspects of the *Aop*/*Foxo* transcriptional programme and is sufficient to extend lifespan. The lifespan-limiting role of *Pnt* appears to be balanced by a requirement for metabolic regulation in young flies, in which the *Aop-Pnt-Foxo* circuit determines expression of metabolic genes, and *Pnt* regulates lipolysis and responses to nutrient stress. Molecular functions are often conserved amongst ETS TFs, prompting us to examine whether other *Drosophila* ETS-coding genes may also affect ageing. We show that five out of eight Drosophila ETS TFs play a role in fly ageing, acting from a range of organs and cells including the intestine, adipose and neurons. We expand the repertoire of lifespan-limiting ETS TFs in *C. elegans*, confirming their conserved function in ageing and revealing that the roles of ETS TFs in physiology and lifespan are conserved throughout the family, both within and between species.

REVIEWS/COMMENTS/ METHODS/EDITORIALS

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REVIEW

Recent advances in understanding the mechanisms determining longevity [version 1; peer review: 3 approved]

Robert Bayersdorf[1,2], Björn Schumacher [1,2]

Author details

Abstract

The field of aging research has progressed significantly over the past decades. Exogenously and endogenously inflicted molecular damage ranging from genotoxic to organellar damage drives the aging process. Repair mechanisms and compensatory responses counteract the detrimental consequences of the various damage types. Here, we discuss recent progress in understanding cellular mechanisms and interconnections between signaling pathways that control longevity. We summarize cell-autonomous and non-cell-autonomous mechanisms that impact the cellular and organismal aging process

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REVIEW

mTOR as a central regulator of lifespan and aging [version 1; peer review: 3 approved]

David Papadopoli[1,2*], Karine Boulay[1,3,4*], Lawrence Kazak [5,6], Michael Pollak[1,2,5,7], Frédérick A. Mallette [3,4,8], Ivan Topisirovic [1,2,6,7], Laura Hulea[3,4,8]

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Abstract

The mammalian/mechanistic target of rapamycin (mTOR) is a key component of cellular metabolism that integrates nutrient sensing with cellular processes that fuel cell growth and proliferation. Although the involvement of the mTOR pathway in regulating life span and aging has been studied extensively in the last decade, the underpinning mechanisms remain elusive. In this review, we highlight the emerging insights that link mTOR to various processes related to aging, such as nutrient sensing, maintenance of proteostasis, autophagy, mitochondrial dysfunction, cellular senescence, and decline in stem cell function.

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Expansion and Cell-Cycle Arrest: Common Denominators of Cellular Senescence

Cellular senescence is a major driver of age-related diseases, and senotherapies are being tested in clinical trials. Despite its popularity, cellular senescence is weakly defined and is frequently referred to as irreversible cell-cycle arrest. In this article we hypothesize that cellular senescence is a phenotype that results from the coordination of two processes: cell expansion and cell-cycle arrest. We provide evidence for the compatibility of the proposed model with recent findings showing senescence in postmitotic tissues, wound healing, obesity, and development. We believe our model also explains why some characteristics of senescence can be found in non-senescent cells. Finally, we propose new avenues for research from our model.

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DNA Damage and Associated DNA Repair Defects in Disease and Premature Aging

Genetic information is constantly being attacked by intrinsic and extrinsic damaging agents, such as reactive oxygen species, atmospheric radiation, environmental chemicals, and chemotherapeutics. If DNA modifications persist, they can adversely affect the polymerization of DNA or RNA, leading to replication fork collapse or transcription arrest, or can serve as mutagenic templates during nucleic acid synthesis reactions. To combat the deleterious consequences of DNA damage, organisms have developed complex repair networks that remove chemical modifications or aberrant base arrangements and restore the genome to its original state. Not surprisingly, inherited or sporadic defects in DNA repair mechanisms can give rise to cellular outcomes that underlie disease and aging, such as transformation, apoptosis, and senescence. In the review here, we discuss several genetic disorders linked to DNA repair defects, attempting to draw correlations between the nature of the accumulating DNA damage and the pathological endpoints, namely cancer, neurological disease, and premature aging.

DNA methylation dynamics in aging: how far are we from understanding the mechanisms?

Fabio Ciccarone [a], Stefano Tagliatesta [b], Paola Caiafa [b], Michele Zampieri [b]

DNA methylation is currently the most promising molecular marker for monitoring aging and predicting life expectancy. However, the mechanisms underlying age-related DNA methylation changes remain mostly undiscovered.

Here we discuss the current knowledge of the dynamic nature of DNA epigenome landscape in mammals, and propose putative molecular mechanisms for aging-associated DNA epigenetic changes. Specifically, we describe age-related variations of methylcytosine and its oxidative derivatives in relation to the dynamics of chromatin structure, histone post-translational modifications and their modulators.

Finally, we are proposing a conceptual framework that could explain the complex nature of the effects of age on DNA methylation patterns. This combines the accumulation of DNA methylation noise and also all of the predictable, site-specific DNA methylation changes.

Gathering information in this area would pave the way for future investigation aimed at establishing a possible causative role of epigenetic mechanisms in aging.

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Revamping the Evolutionary Theories of Aging.

Johnson AA[1], Shokhirev MN[2], Shoshitaishvili B[3].

Author information

Abstract

Radical lifespan disparities exist in the animal kingdom. While the ocean quahog can survive for half a millennium, the mayfly survives for less than 48 hours. The evolutionary theories of aging seek to explain why such stark longevity differences exist and why a deleterious process like aging evolved. The classical mutation accumulation, antagonistic pleiotropy, and disposable soma theories predict that increased extrinsic mortality should select for the evolution of shorter lifespans and vice versa. Most experimental and comparative field studies conform to this prediction. Indeed, animals with extreme longevity (e.g., Greenland shark, bowhead whale, giant tortoise, vestimentiferan tubeworms) typically experience minimal predation. However, data from guppies, nematodes, and computational models show that increased extrinsic mortality can sometimes lead to longer evolved lifespans. The existence of theoretically immortal animals that experience extrinsic mortality - like planarian flatworms, panther worms, and hydra - further challenges classical assumptions. Octopuses pose another puzzle by exhibiting short lifespans and an uncanny intelligence, the latter of which is often associated with longevity and reduced extrinsic mortality. The evolutionary response to extrinsic mortality is likely dependent on multiple interacting factors in the organism, population, and ecology, including food availability, population density, reproductive cost, age-mortality interactions, and the mortality source.

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A Cleaning Crew: The Pursuit of Autophagy in Parkinson's Disease

Pathik Parekh, Nishant Sharma, Anagha Gadepalli, Abhishekh Shahane, Monika Sharma and Amit Khairnar*

Parkinson's disease (PD) is the second-most common neurodegenerative disorder, neuropathologically characterized by the aggregation of misfolded α-synuclein (α-syn) protein, which appears to be central to the onset and progression of PD pathology. Evidence from pioneering studies has highly advocated the existence of impaired autophagy pathways in the brains of PD patients. Autophagy is an evolutionarily conserved, homeostatic mechanism for minimizing abnormal protein aggregates and facilitating organelle turnover. Any aberration in constitutive autophagy activity results in the aggregation of misfolded α-syn, which, in turn, may further inhibit their own degradation—leading to a vicious cycle of neuronal death. Despite the plethora of available literature, there are still lacunas existing in our understanding of the exact cellular interplay between autophagy impairment and α-syn accumulation-mediated neurotoxicity. In this context, clearance of aggregated α-syn via up-regulation of the autophagy–lysosomal pathway could provide a pharmacologically viable approach to the treatment of PD. The present Review highlights the basics of autophagy and detrimental cross-talk between α-syn and chaperone-mediated autophagy, and α-syn and macroautophagy. It also depicts the interaction between α-syn and novel targets, LRRK2 and mTOR, followed by the role of autophagy in PD from a therapeutic perspective. More importantly, it further updates the reader's understanding of various newer therapeutic avenues that may accomplish disease modification via promoting clearance of toxic α-syn through activation of autophagy.

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Artificial Intelligence Based Approaches to Identify Molecular Determinants of Exceptional Health and Life Span-An Interdisciplinary Workshop at the National Institute on Aging

Jason H. Moore[1], Nalini Raghavachari[2*] and Workshop Speakers[†]

Artificial intelligence (AI) has emerged as a powerful approach for integrated analysis of the rapidly growing volume of multi-omics data, including many research and clinical tasks such as prediction of disease risk and identification of potential therapeutic targets. However, the potential for AI to facilitate the identification of factors contributing to human exceptional health and life span and their translation into novel interventions for enhancing health and life span has not yet been realized. As researchers on aging acquire large scale data both in human cohorts and model organisms, emerging opportunities exist for the application of AI approaches to untangle the complex physiologic process(es) that modulate health and life span. It is expected that efficient and novel data mining tools that could unravel molecular mechanisms and causal pathways associated with exceptional health and life span could accelerate the discovery of novel therapeutics for healthy aging. Keeping this in mind, the National Institute on Aging (NIA) convened an interdisciplinary workshop titled "Contributions of Artificial Intelligence to Research on Determinants and Modulation of Health Span and Life Span" in August 2018. The workshop involved experts in the fields of aging, comparative biology, cardiology, cancer, and computational science/AI who brainstormed ideas on how AI can be leveraged for the analyses of large-scale data sets from human epidemiological studies and animal/model organisms to close the current knowledge gaps in processes that drive exceptional life and health span. This report summarizes the discussions and recommendations from the workshop on future application of AI approaches to advance our understanding of human health and life span.

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An overview of two decades of diet restriction studies using *Drosophila*

Dietary restriction (DR) is a potent forerunner in aging studies capable of influencing lifespan and improving health in various model organisms even in their old age. Despite the importance of protein and carbohydrates in the diet (regulation of fecundity and body maintenance respectively), different ratio based combinations of these components has played a major role in lifespan extension studies. In spite of differences existing in dietary protocols across laboratories, diet manipulations have evolved as a major area of research in *Drosophila* lifespan studies, prominently shedding light on the multi-faceted process over the last two decades. Here, we review various advances and technicalities involved in understanding the DR-mediated lifespan alongside discussing the pros and cons of various existing approaches/diets used across labs. The current review also focuses on the importance of life-stage specific DR implementation and their influence on the life-history traits including lifespan and fecundity, by taking examples of results from different studies comprising diet dilution, calorie restriction, protein restriction, carbohydrate: protein ratios and the modulations in various minor diet components. We thereby intend to gather the major advances made in these fields alongside reviewing the practical implementations that need to be made to get a better view of the DR-mediated lifespan studies.

OTHER RESEARCH

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GRP78 promotes stemness in normal and neoplastic cells

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ABSTRACT

Reliable approaches to identify stem cell mechanisms that mediate aggressive cancer could have great therapeutic value, based on the growing evidence of embryonic signatures in metastatic cancers. However, how to best identify and target stem-like mechanisms aberrantly acquired by cancer cells has been challenging. We harnessed the power of reprogramming to examine GRP78, a chaperone protein generally restricted to the endoplasmic reticulum in normal tissues, but which is expressed on the cell surface of human embryonic stem cells and many cancer types. We have discovered that (1) cell surface GRP78 (sGRP78) is expressed on iPSCs and is important in reprogramming, (2) sGRP78 promotes cellular functions in both pluripotent and breast cancer cells (3) overexpression of GRP78 in breast cancer cells leads to an induction of a $CD24^{-}/CD44^{+}$ tumor initiating cell (TIC) population (4) $sGRP78^{+}$ breast cancer cells are enriched for stemness genes and appear to be a subset of TICs (5) $sGRP78^{+}$ breast cancer cells show an enhanced ability to seed metastatic organ sites *in vivo*. These collective findings show that GRP78 has important functions in regulating both pluripotency and oncogenesis, and suggest that sGRP78 marks a stem-like population in breast cancer cells that has increased metastatic potential *in vivo*.

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Dietary methionine influences therapy in mouse cancer models and alters human metabolism

Nutrition exerts considerable effects on health, and dietary interventions are commonly used to treat diseases of metabolic aetiology. Although cancer has a substantial metabolic component[1], the principles that define whether nutrition may be used to influence outcomes of cancer are unclear[2]. Nevertheless, it is established that targeting metabolic pathways with pharmacological agents or radiation can sometimes lead to controlled therapeutic outcomes. By contrast, whether specific dietary interventions can influence the metabolic pathways that are targeted in standard cancer therapies is not known. Here we show that dietary restriction of the essential amino acid methionine—the reduction of which has anti-ageing and anti-obesogenic properties—influences cancer outcome, through controlled and reproducible changes to one-carbon metabolism. This pathway metabolizes methionine and is the target of a variety of cancer interventions that involve chemotherapy and radiation. Methionine restriction produced therapeutic responses in two patient-derived xenograft models of chemotherapy-resistant RAS-driven colorectal cancer, and in a mouse model of autochthonous soft-tissue sarcoma driven by a G12D mutation in KRAS and knockout of p53 ($Kras^{G12D/+}$;$Trp53^{-/-}$) that is resistant to radiation. Metabolomics revealed that the therapeutic mechanisms operate via tumour-cell-autonomous effects on flux through one-carbon metabolism that affects redox and nucleotide metabolism—and thus interact with the antimetabolite or radiation intervention. In a controlled and tolerated feeding study in humans, methionine restriction resulted in effects on systemic metabolism that were similar to those obtained in mice. These findings provide evidence that a targeted dietary manipulation can specifically affect tumour-cell metabolism to mediate broad aspects of cancer outcome.