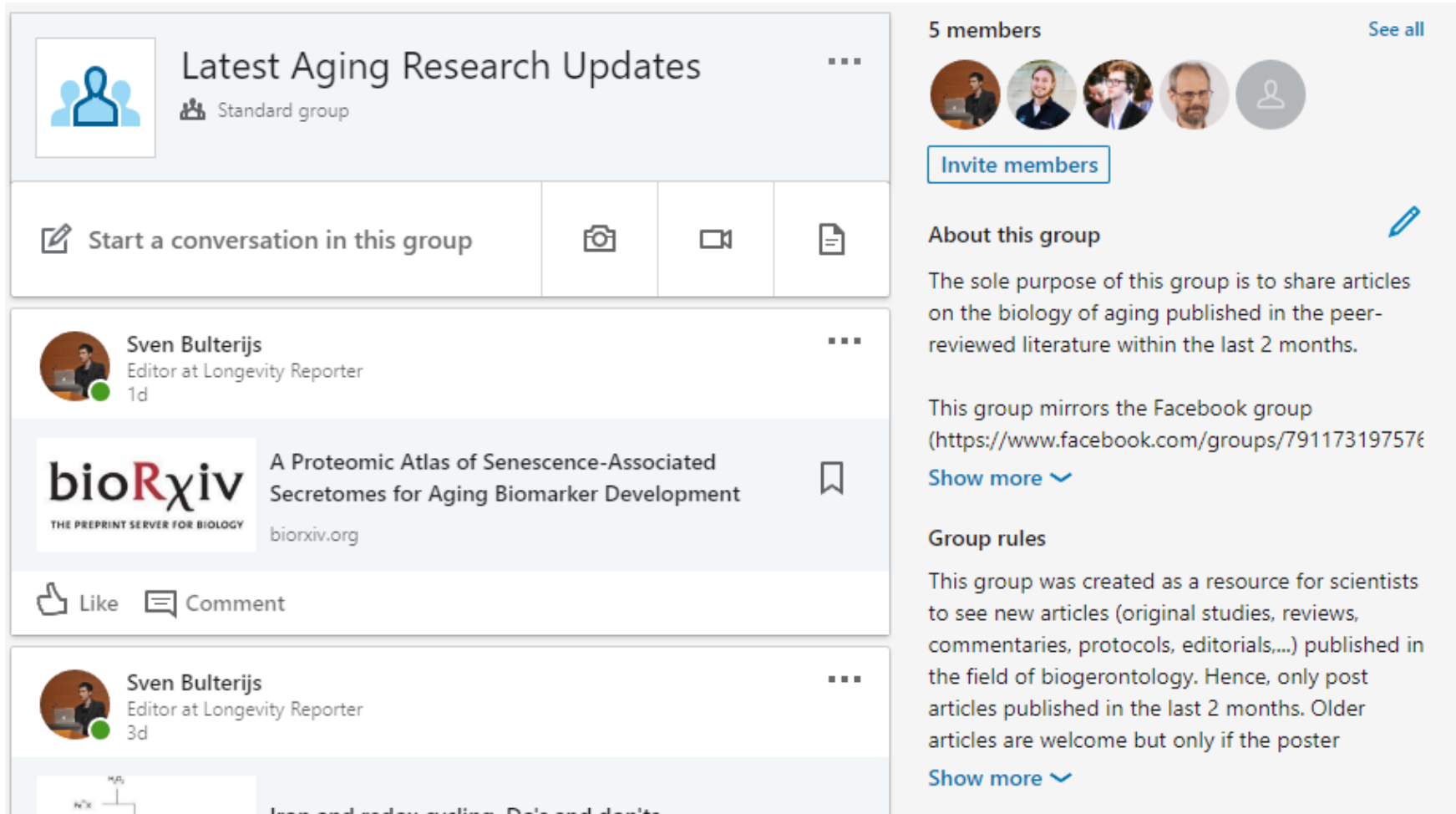




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A Proteomic Atlas of Senescence-Associated Secretomes for Aging Biomarker Development
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Iron and redox cycling: Do's and don'ts

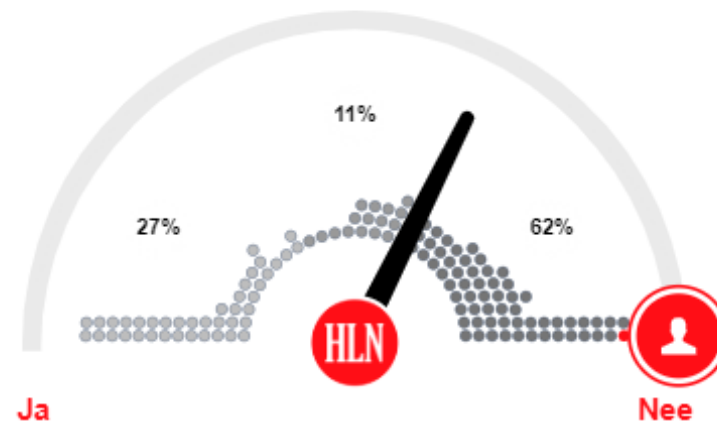
62% of respondents voted against banning all animal testing

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HET LAATSTE NIEUWS

Catalent puts down a bet on the future of gene therapy



Lisa Urquhart

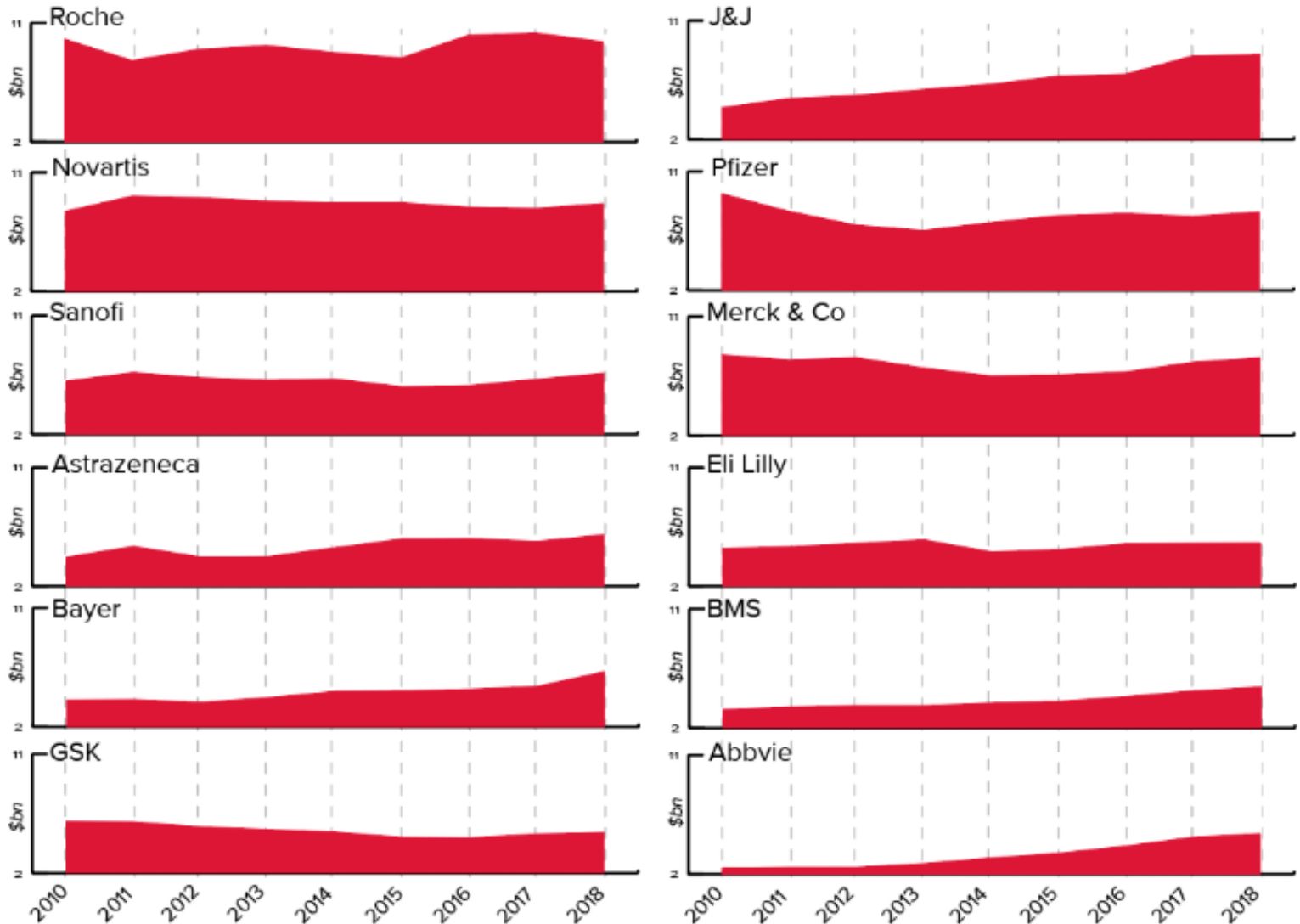


As the number of cell and gene therapies in development increases so must manufacturing capacity, leaving biopharma with a crucial decision; buy or build? With yesterday's \$1.2bn all-cash takeout of the manufacturer Paragon Biosciences, Catalent is betting on companies opting for buy. And Catalent is not alone in seeing the promise of hoovering up available gene and cell therapy contract manufacturing businesses; in March Thermo Fisher bought Brammer Bio for \$1.7bn. Catalent's move on the private equity-backed Paragon came days after Paragon opened a new manufacturing facility in Baltimore, and on the same day that it announced the extension of an existing relationship with Sarepta to build more gene therapy manufacturing capacity. Both events bode well for Catalent, which clearly has an eye on the long-term forecast claiming a \$40bn addressable market for gene therapy. As for the near term, one rationale for the deal comes in the form of the \$200m Paragon is expected to bank this year from manufacturing contracts and the promises of much more to come in future. Catalent is getting in early on gene therapy consolidation, and with reports of demand for gene therapy manufacturing outstripping supply there could be more such deals.

Selected cell and gene therapy manufacturing deals				
Date	Aquirer	Target	Deal type	Price
Apr 2019	Catalent	Paragon Bioservices	Acquisition	\$1.2bn
Mar 2019	Thermo Fisher	Brammer Bio	Acquisition	\$1.7bn
Jan 2019	Hitachi Chemical	Apceth Biopharma	Acquisition	\$86m
Oct 2018	Lonza	Octane Biotech	Controlling stake	-
May 2017	Lonza	Pharmacell	Acquisition	-

Swiss big pharmas top the research spending tables

Big Pharma R&D spend (\$bn)



Biogen cans plan to test aducanumab in Alzheimer's prevention

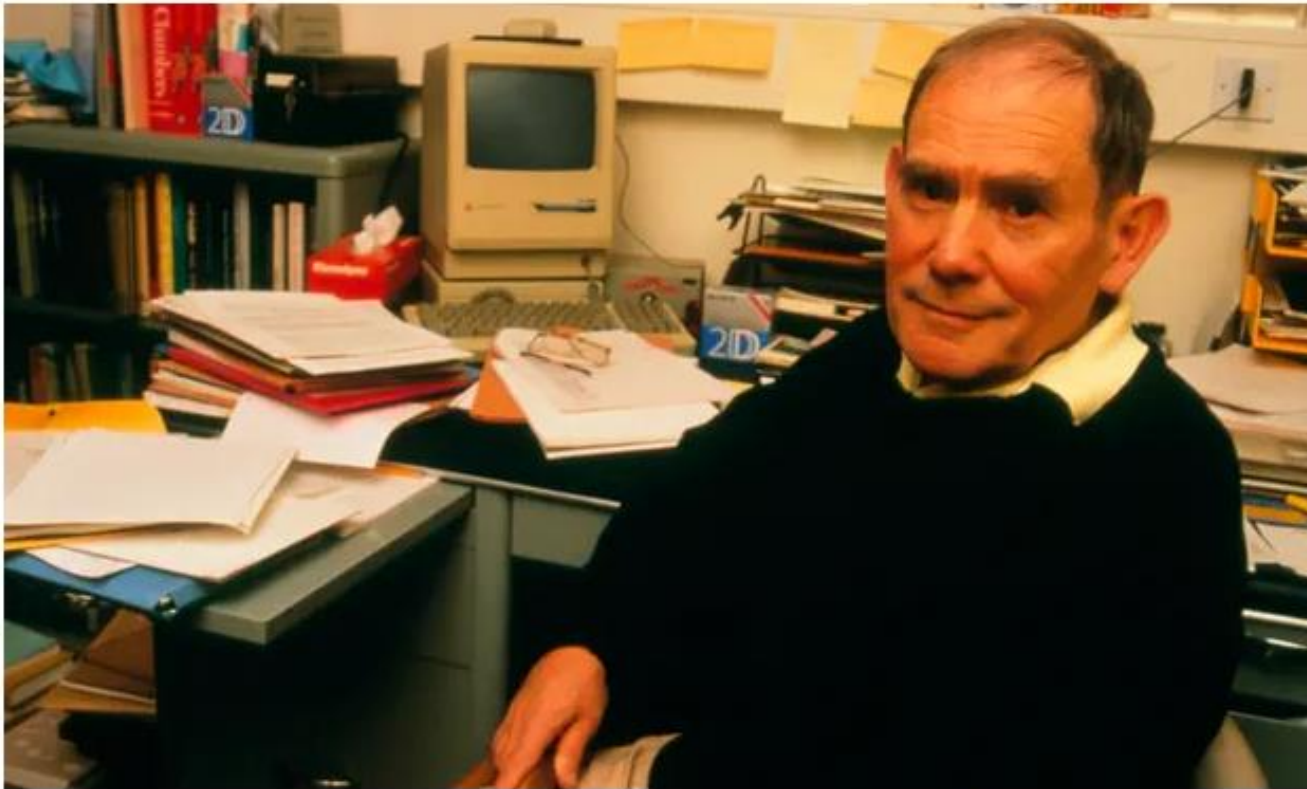
by **Nick Paul Taylor** | Apr 24, 2019 10:30am



Biogen continues to list Alzheimer's and dementia as a key growth area. (Biogen)

Sydney Brenner obituary

Nobel prize-winning biologist whose research into a tiny nematode worm led to critical insights into human disease



▲ Sydney Brenner was often described as the 'enfant terrible of molecular biology'. Photograph: Science Photo Library

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[Chembiochem](#). 2019 Apr 23. doi: 10.1002/cbic.201900158. [Epub ahead of print]

Biocatalytic Reversal of Advanced Glycation End Product Modification.


[Kim NY](#)¹, [Goddard TN](#)¹, [Sohn S](#)¹, [Spiegel DA](#)¹, [Crawford J](#)².

⊕ Author information

Abstract

Advanced glycation end products (AGEs) are a heterogeneous group of molecules that emerge from the condensation of sugars and proteins via the Maillard reaction. Despite a significant number of studies showing strong associations between AGEs and the pathologies of aging-related illnesses, it has been a challenge to establish AGEs as causal agents primarily due to the lack of tools in reversing AGE modifications at the molecular level. Here, we show that MnmC, an enzyme involved in a bacterial tRNA-modification pathway, is capable of reversing the AGEs carboxyethyl-lysine (CEL) and carboxymethyl-lysine (CML) back to their native lysine structure. Combining structural homology analysis, site-directed mutagenesis, and protein domain dissection studies, we generated a variant of MnmC with improved catalytic properties against CEL in free amino acid form. We show that this enzyme variant is also active on a CEL-modified peptidomimetic and an AGE-containing peptide that has been established as an authentic ligand of the receptor for AGEs (RAGE). Our data demonstrate that MnmC variants are promising lead catalysts toward the development of AGE-reversal tools and a better understanding of AGE biology.

A Proteomic Atlas of Senescence-Associated Secretomes for Aging Biomarker Development

 Nathan Basisty, Abhijit Kale, Okhee Jeon, Chisaka Kuehnemann, Therese Payne, Chirag Rao, Anja Holtz, Samah Shah, Luigi Ferrucci, Judith Campisi, Birgit Schilling

doi: <https://doi.org/10.1101/604306>

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

Abstract

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SUMMARY

The senescence-associated secretory phenotype (SASP) has recently emerged as both a driver of, and promising therapeutic target for, multiple age-related conditions, ranging from neurodegeneration to cancer. The complexity of the SASP, typically monitored by a few dozen secreted proteins, has been greatly underappreciated, and a small set of factors cannot explain the diverse phenotypes it produces *in vivo*. Here, we present ‘SASP Atlas’, a comprehensive proteomic database of soluble and exosome SASP factors originating from multiple senescence inducers and cell types. Each profile consists of hundreds of largely distinct proteins, but also includes a subset of proteins elevated in all SASPs. Based on our analyses, we propose several candidate biomarkers of cellular senescence, including GDF15, STC1 and SERPINS. This resource will facilitate identification of proteins that drive specific senescence-associated phenotypes and catalog potential senescence biomarkers to assess the burden, originating stimulus and tissue of senescent cells *in vivo*.

A Human Tissue-Specific Transcriptomic Analysis Reveals that Ageing Hinders Cancer and Boosts Cellular Senescence

Kasit Chatsirisupachai, Daniel Palmer, Susana Ferreira, João Pedro de Magalhães

doi: <https://doi.org/10.1101/595041>

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

Abstract

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Abstract

Ageing is the biggest risk factor for cancer, but the mechanisms linking these two processes remain unclear. We compared genes differentially expressed with age and genes differentially expressed in cancer among nine human tissues. In most tissues, ageing and cancer gene expression surprisingly changed in the opposite direction. These overlapping gene sets were related to several processes, mainly cell cycle and the immune system. Moreover, cellular senescence signatures derived from a meta-analysis changed in the same direction as ageing and in the opposite direction of cancer signatures. Therefore, transcriptomic changes in ageing and cellular senescence might relate to a decrease in cell proliferation, while cancer transcriptomic changes shift towards an increase in cell division. Our results highlight the complex relationship between ageing, cancer and cellular senescence and suggest that in most human tissues ageing processes and senescence act in tandem while being detrimental to cancer. Our work challenges the traditional view concerning the relationship between cancer and ageing and suggests that ageing processes may hinder cancer development.

Targeting senescent cells alleviates obesity-induced metabolic dysfunction

Adipose tissue inflammation and dysfunction are associated with obesity-related insulin resistance and diabetes, but mechanisms underlying this relationship are unclear. Although senescent cells accumulate in adipose tissue of obese humans and rodents, a direct pathogenic role for these cells in the development of diabetes remains to be demonstrated. Here, we show that reducing senescent cell burden in obese mice, either by activating drug-inducible “suicide” genes driven by the p16^{Ink4a} promoter or by treatment with senolytic agents, alleviates metabolic and adipose tissue dysfunction. These senolytic interventions improved glucose tolerance, enhanced insulin sensitivity, lowered circulating inflammatory mediators, and promoted adipogenesis in obese mice. Elimination of senescent cells also prevented the migration of transplanted monocytes into intra-abdominal adipose tissue and reduced the number of macrophages in this tissue. In addition, microalbuminuria, renal podocyte function, and cardiac diastolic function improved with senolytic therapy. Our results implicate cellular senescence as a causal factor in obesity-related inflammation and metabolic derangements and show that emerging senolytic agents hold promise for treating obesity-related metabolic dysfunction and its complications.

Pharmacological clearance of senescent cells improves survival and recovery in aged mice following acute myocardial infarction

Anna Walaszczyk, Emily Dookun, Rachael Redgrave, Simon Tual-Chalot, Stella Victorelli, Ioakim Spyridopoulos, Andrew Owens, Helen M. Arthur, João F. Passos ✉, Gavin D. Richardson ✉

Cardiovascular disease is the leading cause of death in individuals over 60 years old. Aging is associated with an increased prevalence of coronary artery disease and a poorer prognosis following acute myocardial infarction (MI). With age, senescent cells accumulate in tissues, including the heart, and contribute to age-related pathologies. However, the role of senescence in recovery following MI has not been investigated. In this study, we demonstrate that treatment of aged mice with the senolytic drug, navitoclax, eliminates senescent cardiomyocytes and attenuates profibrotic protein expression in aged mice. Importantly, clearance of senescent cells improved myocardial remodelling and diastolic function as well as overall survival following MI. These data provide proof-of-concept evidence that senescent cells are major contributors to impaired function and increased mortality following MI and that senolytics are a potential new therapeutic avenue for MI.





Cardiomyocyte glucocorticoid and mineralocorticoid receptors directly and antagonistically regulate heart disease in mice

Stress is increasingly associated with heart dysfunction and is linked to higher mortality rates in patients with cardiometabolic disease. Glucocorticoids are primary stress hormones that regulate homeostasis through two nuclear receptors, the glucocorticoid receptor (GR) and mineralocorticoid receptor (MR), both of which are present in cardiomyocytes. To examine the specific and coordinated roles that these receptors play in mediating the direct effects of stress on the heart, we generated mice with cardiomyocyte-specific deletion of GR (cardioGRKO), MR (cardioMRKO), or both GR and MR (cardioGRMRdKO). The cardioGRKO mice spontaneously developed cardiac hypertrophy and left ventricular systolic dysfunction and died prematurely from heart failure. In contrast, the cardioMRKO mice exhibited normal heart morphology and function. Despite the presence of myocardial stress, the cardioGRMRdKO mice were resistant to the cardiac remodeling, left ventricular dysfunction, and early death observed in the cardioGRKO mice. Gene expression analysis revealed the loss of gene changes associated with impaired Ca^{2+} handling, increased oxidative stress, and enhanced cell death and the presence of gene changes that limited the hypertrophic response and promoted cardiomyocyte survival in the double knockout hearts. Reexpression of MR in cardioGRMRdKO hearts reversed many of the cardioprotective gene changes and resulted in cardiac failure. These findings reveal a critical role for balanced cardiomyocyte GR and MR stress signaling in cardiovascular health. Therapies that shift stress signaling in the heart to favor more GR and less MR activity may provide an improved approach for treating heart disease.

DNA damage-induced PARP1 activation confers cardiomyocyte dysfunction through NAD⁺ depletion in experimental atrial fibrillation

Atrial fibrillation (AF) is the most common clinical tachyarrhythmia with a strong tendency to progress in time. AF progression is driven by derailment of protein homeostasis, which ultimately causes contractile dysfunction of the atria. Here we report that tachypacing-induced functional loss of atrial cardiomyocytes is precipitated by excessive poly(ADP)-ribose polymerase 1 (PARP1) activation in response to oxidative DNA damage. PARP1-mediated synthesis of ADP-ribose chains in turn depletes nicotinamide adenine dinucleotide (NAD⁺), induces further DNA damage and contractile dysfunction. Accordingly, NAD⁺ replenishment or PARP1 depletion precludes functional loss. Moreover, inhibition of PARP1 protects against tachypacing-induced NAD⁺ depletion, oxidative stress, DNA damage and contractile dysfunction in atrial cardiomyocytes and *Drosophila*. Consistently, cardiomyocytes of persistent AF patients show significant DNA damage, which correlates with PARP1 activity. The findings uncover a mechanism by which tachypacing impairs cardiomyocyte function and implicates PARP1 as a possible therapeutic target that may preserve cardiomyocyte function in clinical AF.

SIRT6 Is Responsible for More Efficient DNA Double-Strand Break Repair in Long-Lived Species

Xiao Tian • Denis Firsanov • Zihui Zhang • ... Vadim N. Gladyshev • Andrei Seluanov   • Vera Gorbunova  ¹¹  • [Show all authors](#) • [Show footnotes](#)

DNA repair has been hypothesized to be a longevity determinant, but the evidence for it is based largely on accelerated aging phenotypes of DNA repair mutants. Here, using a panel of 18 rodent species with diverse lifespans, we show that more robust DNA double-strand break (DSB) repair, but not nucleotide excision repair (NER), coevolves with longevity. Evolution of NER, unlike DSB, is shaped primarily by sunlight exposure. We further show that the capacity of the SIRT6 protein to promote DSB repair accounts for a major part of the variation in DSB repair efficacy between short- and long-lived species. We dissected the molecular differences between a weak (mouse) and a strong (beaver) SIRT6 protein and identified five amino acid residues that are fully responsible for their differential activities. Our findings demonstrate that DSB repair and SIRT6 have been optimized during the evolution of longevity, which provides new targets for anti-aging interventions.

Higher serum levels of fibroblast growth factor 21 in old patients with cachexia.

Franz K¹, Ost M², Otten L¹, Herpich C³, Coleman V², Endres AS⁴, Klaus S⁵, Müller-Werdan U⁴, Norman K⁶.

⊕ Author information

Abstract

OBJECTIVE: Fibroblast growth factor (FGF)21 is promptly induced by short fasting in animal models to regulate glucose and fat metabolism. Data on FGF21 in humans are inconsistent and FGF21 has not yet been investigated in old patients with cachexia, a complex syndrome characterized by inflammation and weight loss. The aim of this study was to explore the association of FGF21 with cachexia in old patients compared with their healthy counterparts.

METHODS: Serum FGF21 and its inactivating enzyme fibroblast activation protein (FAP)- α were measured with enzyme-linked immunoassays. Cachexia was defined as $\geq 5\%$ weight loss in the previous 3 mo and concurrent anorexia (Council on Nutrition appetite questionnaire).

RESULTS: We included 103 patients with and without cachexia (76.9 ± 5.2 y of age) and 56 healthy controls (72.9 ± 5.9 y of age). Cachexia was present in 16.5% of patients. These patients had significantly higher total FGF21 levels than controls (952.1 ± 821.3 versus 525.2 ± 560.3 pg/mL; $P = 0.012$) and the lowest FGF21 levels (293.3 ± 150.9 pg/mL) were found in the control group (global $P < 0.001$). Although FAP- α did not differ between the three groups (global $P = 0.082$), bioactive FGF21 was significantly higher in patients with cachexia (global $P = 0.002$). Risk factor-adjusted regression analyses revealed a significant association between cachexia and total ($\beta = 649.745$ pg/mL; $P < 0.001$) and bioactive FGF21 ($\beta = 393.200$ pg/mL; $P < 0.001$), independent of sex, age, and body mass index.

CONCLUSIONS: Patients with cachexia exhibited the highest FGF21 levels. Clarification is needed to determine whether this is an adaptive response to nutrient deprivation in disease-related cachexia or whether the increased FGF21 values contribute to the catabolic state.

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4E-BP1 and 4E-BP2 double knockout mice are protected from aging-associated sarcopenia.

Le Bacquer O¹, Combe K¹, Patrac V¹, Ingram B², Combaret L¹, Dardevet D¹, Montaurier C¹, Salles J¹, Giraudet C¹, Guillet C¹, Sonenberg N³, Boirie Y^{1,4}, Walrand S¹.

⊕ Author information

Abstract

BACKGROUND: Sarcopenia is the loss of muscle mass/function that occurs during the aging process. The links between mechanistic target of rapamycin (mTOR) activity and muscle development are largely documented, but the role of its downstream targets in the development of sarcopenia is poorly understood. Eukaryotic initiation factor 4E-binding proteins (4E-BPs) are targets of mTOR that repress mRNA translation initiation and are involved in the control of several physiological processes. However, their role in skeletal muscle is still poorly understood. The goal of this study was to assess how loss of 4E-BP1 and 4E-BP2 expression impacts skeletal muscle function and homeostasis in aged mice and to characterize the associated metabolic changes by metabolomic and lipidomic profiling.

METHODS: Twenty-four-month-old wild-type and whole body 4E-BP1/4E-BP2 double knockout (DKO) mice were used to measure muscle mass and function. Protein homeostasis was measured *ex vivo* in extensor digitorum longus by incorporation of I-[U-¹⁴C]phenylalanine, and metabolomic and lipidomic profiling of skeletal muscle was performed by Metabolon, Inc.

RESULTS: The 4E-BP1/2 DKO mice exhibited an increase in muscle mass that was associated with increased grip strength ($P < 0.05$). Protein synthesis was higher under both basal (+102%, $P < 0.05$) and stimulated conditions (+65%, $P < 0.05$) in DKO skeletal muscle. Metabolomic and complex lipid analysis of skeletal muscle revealed robust differences pertaining to amino acid homeostasis, carbohydrate abundance, and certain aspects of lipid metabolism. In particular, levels of most free amino acids were lower within the 4E-BP1/2 DKO muscle. Interestingly, although glucose levels were unchanged, differences were observed in the isobaric compound maltitol/lactitol (33-fold increase, $P < 0.01$) and in several additional carbohydrate compounds. 4E-BP1/2 depletion also resulted in accumulation of medium-chain acylcarnitines and a 20% lower C2/C0 acylcarnitine ratio ($P < 0.01$) indicative of reduced β -oxidation.

CONCLUSIONS: Taken together, these findings demonstrate that deletion of 4E-BPs is associated with perturbed energy metabolism in skeletal muscle and could have beneficial effects on skeletal muscle mass and function in aging mice. They also identify 4E-BPs as potential targets for the treatment of sarcopenia.

mTORC1 underlies age-related muscle fiber damage and loss by inducing oxidative stress and catabolism

Aging leads to skeletal muscle atrophy (i.e., sarcopenia), and muscle fiber loss is a critical component of this process. The mechanisms underlying these age-related changes, however, remain unclear. We show here that mTORC1 signaling is activated in a subset of skeletal muscle fibers in aging mouse and human, colocalized with fiber damage.

Activation of mTORC1 in TSC1 knockout mouse muscle fibers increases the content of morphologically abnormal mitochondria and causes progressive oxidative stress, fiber damage, and fiber loss over the lifespan. Transcriptomic profiling reveals that mTORC1's activation increases the expression of growth differentiation factors (GDF3, 5, and 15), and of genes involved in mitochondrial oxidative stress and catabolism. We show that increased GDF15 is sufficient to induce oxidative stress and catabolic changes, and that mTORC1 increases the expression of GDF15 via phosphorylation of STAT3. Inhibition of mTORC1 in aging mouse decreases the expression of GDFs and STAT3's phosphorylation in skeletal muscle, reducing oxidative stress and muscle fiber damage and loss. Thus, chronically increased mTORC1 activity contributes to age-related muscle atrophy, and GDF signaling is a proposed mechanism.

Age and prior exercise in vivo determine the subsequent in vitro molecular profile of myoblasts and non-myogenic cells derived from human skeletal muscle

The decline in skeletal muscle regenerative capacity with age is partly attributed to muscle stem cell (satellite cell) dysfunction. Recent evidence has pointed to a strong interaction between myoblasts and fibroblasts, but the influence of age on this interaction is unknown. Additionally, while the native tissue environment is known to determine the properties of myogenic cells in vitro, how the ageing process alters this cell memory has not been established at the molecular level. We recruited 12 young and 12 elderly women, who performed a single bout of heavy resistance exercise with the knee extensor muscles of one leg. 5 days later, muscle biopsies were collected from both legs and myogenic cells and non-myogenic cells were isolated for in vitro experiments with mixed or separated cells, and analysed by immunostaining and RT-PCR. A lower myogenic fusion index was detected in the cells from the old vs. young women, in association with differences in gene expression levels of key myogenic regulatory factors and senescence, which were further altered by performing exercise prior to tissue sampling. Co-culture with non-myogenic cells from the elderly lead to a higher myogenic differentiation index compared to non-myogenic cells from the young. These findings show that the in vitro phenotype and molecular profile of human skeletal muscle myoblasts and fibroblasts is determined by the age and exercise state of the original in vivo environment and help explain how exercise can enhance muscle stem cell function in old age.

Aging (Albany, NY), 2019 Apr 24. doi: 10.18632/aging.101914. [Epub ahead of print]

Cell-autonomous and non-autonomous roles of *daf-16* in muscle function and mitochondrial capacity in aging *C. elegans*.

Wang H^{#1,2}, Webster P^{#1,2}, Chen L^{2,3}, Fisher AL^{1,2,4,5}.

⊕ Author information

Abstract

Sarcopenia, defined as the loss of skeletal muscle mass and strength, contributes to disability and health-related conditions with aging. In vitro studies indicate that age-related mitochondrial dysfunction could play a central role in the development and progression of sarcopenia, but because of limitations in the methods employed, how aging affects muscle mitochondrial function in vivo is not fully understood. We use muscle-targeted fluorescent proteins and the ratiometric ATP reporter, ATeam, to examine changes in muscle mitochondrial mass and morphology, and intracellular ATP levels in *C. elegans*. We find that the preserved muscle function in aging *daf-2* mutants is associated with higher muscle mitochondrial mass, preserved mitochondrial morphology, and higher levels of intracellular ATP. These phenotypes require the *daf-16*/FOXO transcription factor. Via the tissue-specific rescue of *daf-16*, we find that *daf-16* activity in either muscle or neurons is sufficient to enhance muscle mitochondrial mass, whereas *daf-16* activity in the muscle is required for the enhanced muscle function and mobility of the *daf-2* mutants. Finally, we show through the use of drugs known to enhance mitochondrial activity that augmenting mitochondrial function leads to improved mobility during aging. These results suggest an important role for mitochondrial function in muscle aging.

Exp Gerontol. 2019 Apr 16;122:25-33. doi: 10.1016/j.exger.2019.04.008. [Epub ahead of print]

Inhibition of TLR9 attenuates skeletal muscle fibrosis in aged sarcopenic mice via the p53/SIRT1 pathway.

Lyu AK¹, Zhu SY¹, Chen JL¹, Zhao YX¹, Pu D¹, Luo C¹, Lyu Q¹, Fan Z¹, Sun Y¹, Wu J¹, Zhao KX¹, Xiao Q².

⊕ Author information

Abstract

Sarcopenia is an age-related syndrome characterized by a gradual loss of muscle mass and function, but its pathophysiological mechanism remains unclear. Skeletal muscle extracellular matrix (ECM) remodeling is an important pathological change in sarcopenia, and fibrosis is the most obvious manifestation of this change. We found that the expression of the immunoreceptor Toll-like receptor 9 (TLR9) is significantly increased in skeletal muscle in aged mice and is positively related to muscle fibrosis. Moreover, in previous reports, the longevity gene Sirt1 was reported to attenuate ECM deposition and improve muscle function. In this study, we hypothesized that TLR9 modulated skeletal muscle fibrosis via Sirt1. We used TLR9 knockout (TLR9 KO) mice and C57 mice, and grip strength and body composition were compared at different ages. We found that TLR9 knockout significantly attenuated skeletal muscle fibrosis and improved muscle function in aged mice. Furthermore, silent information regulator 1 (Sirt1) activity in mice was inhibited by Ex527, which is a specific inhibitor of Sirt1. Negative Sirt1 regulation via the activation of TLR9-related signaling pathways participated in skeletal muscle fibrosis in the sarcopenic mice, and this process might be mediated by the Sirt1/Smad signaling pathway. Our findings revealed that fibrosis changes in the gastrocnemius muscle in sarcopenic mice are closely related to TLR9 activation, and TLR9 modulation could be a therapeutic strategy for combating sarcopenia during aging.

PLoS One. 2019 Apr 25;14(4):e0215490. doi: 10.1371/journal.pone.0215490. eCollection 2019.

Applying hydrodynamic pressure to efficiently generate induced pluripotent stem cells via reprogramming of centenarian skin fibroblasts.

[Vosough M¹](#), [Ravaioli F²](#), [Zabulica M³](#), [Capri M^{2,4}](#), [Garagnani P^{2,4,5,6}](#), [Franceschi C^{2,7}](#), [Piccand J⁸](#), [Kraus MR⁸](#), [Kannisto K³](#), [Gramignoli R³](#), [Strom SC³](#).

Author information

Abstract

Induced pluripotent stem cell (iPSC)-technology is an important platform in medicine and disease modeling. Physiological degeneration and disease onset are common occurrences in the aging population. iPSCs could offer regenerative medical options for age-related degeneration and disease in the elderly. However, reprogramming somatic cells from the elderly is inefficient when successful at all. Perhaps due to their low rates of replication in culture, traditional transduction and reprogramming approaches with centenarian fibroblasts met with little success. A simple and reproducible reprogramming process is reported here which enhances interactions of the cells with the viral vectors that leads to improved iPSC generation. The improved methods efficiently generates fully reprogrammed iPSC lines from 105-107 years old subjects in feeder-free conditions using an episomal, Sendai-Virus (SeV) reprogramming vector expressing four reprogramming factors. In conclusion, dermal fibroblasts from human subjects older than 100 years can be efficiently and reproducibly reprogrammed to fully pluripotent cells with minor modifications to the standard reprogramming procedures. Efficient generation of iPSCs from the elderly may provide a source of cells for the regeneration of tissues and organs with autologous cells as well as cellular models for the study of aging, longevity and age-related diseases.

Stem cell competition orchestrates skin homeostasis and ageing

Stem cells underlie tissue homeostasis, but their dynamics during ageing—and the relevance of these dynamics to organ ageing—remain unknown. Here we report that the expression of the hemidesmosome component collagen XVII (COL17A1) by epidermal stem cells fluctuates physiologically through genomic/oxidative stress-induced proteolysis, and that the resulting differential expression of COL17A1 in individual stem cells generates a driving force for cell competition. In vivo clonal analysis in mice and in vitro 3D modelling show that clones that express high levels of COL17A1, which divide symmetrically, outcompete and eliminate adjacent stressed clones that express low levels of COL17A1, which divide asymmetrically. Stem cells with higher potential or quality are thus selected for homeostasis, but their eventual loss of COL17A1 limits their competition, thereby causing ageing. The resultant hemidesmosome fragility and stem cell delamination deplete adjacent melanocytes and fibroblasts to promote skin ageing. Conversely, the forced maintenance of COL17A1 rescues skin organ ageing, thereby indicating potential angles for anti-ageing therapeutic intervention.

Aging (Albany NY), 2019 Apr 13;11(7):2098-2110. doi: 10.18632/aging.101903.

In mice transgenic for IGF1 under keratin-14 promoter, lifespan is decreased and the rates of aging and thymus involution are accelerated.

[Anisimov VN](#)¹, [Labunets IF](#)², [Popovich IG](#)¹, [Tyndyk ML](#)¹, [Yurova MN](#)¹, [Golubev AG](#)¹.

⊕ Author information

Abstract

IGF1 signaling is supposedly a key lifespan determinant in metazoans. However, controversial lifespan data were obtained with different means used to modify IGF1 or its receptor (IGF1R) expression in mice. The emerging puzzle lacks pieces of evidence needed to construct a coherent picture. We add to the available evidence by using the Gompertz model (GM), with account for the artifactual component of the Strehler-Mildvan correlation between its parameters, to compare the survival patterns of female FVB/N and FVB/N-derived K14/mIGF1 mice. In K14/mIGF1 vs. FVB/N mice, the rate of aging (γ) is markedly increased without concomitant changes in the initial mortality (μ_0). In published cases where IGF1 signaling was altered by modifying liver or muscle IGF1 or whole body IGF1R expression, lifespan changes are attributable to μ_0 . The accelerated aging and associated tumor yield in K14/mIGF1 mice are consistent with the finding that the age-associated decreases in thymus weight and serum thymulin are accelerated in K14/mIGF1 mice. Our results underscore the importance of accounting for the mathematical artifacts of data fitting to GM in attempts to resolve discrepancies in survival data and to differentiate the contributions of the initial mortality and the rate of aging to changes in lifespan.

[Biochem Biophys Res Commun](#). 2019 Apr 17. pii: S0006-291X(19)30658-8. doi: 10.1016/j.bbrc.2019.04.036. [Epub ahead of print]

Inhibition of GIP signaling extends lifespan without caloric restriction.

[Hoizumi M](#)¹, [Sato T](#)¹, [Shimizu T](#)¹, [Kato S](#)¹, [Tsukiyama K](#)¹, [Narita T](#)¹, [Fujita H](#)¹, [Morii T](#)¹, [Sassa MH](#)², [Seino Y](#)³, [Yamada Y](#)⁴.

⊕ Author information

Abstract

AIMS/INTRODUCTION: Caloric restriction (CR) promotes longevity and exerts anti-aging effects by increasing Sirtuin production and activation. Gastric inhibitory polypeptide (GIP), a gastrointestinal peptide hormone, exerts various effects on pancreatic β -cells and extra-pancreatic tissues. GIP promotes glucose-dependent augmentation of insulin secretion and uptake of nutrients into the adipose tissue.

MATERIALS AND METHODS: *Gipr*^{-/-} and *Gipr*^{+/+} mice were used for lifespan analysis, behavior experiments and gene expression of adipose tissue and muscles. 3T3-L1 differentiated adipocytes were used for Sirt1 and Nampt expression followed by treatment with GIP and α -lipoic acid.

RESULTS: We observed that GIP receptor-knockout (*Gipr*^{-/-}) mice fed normal diet showed an extended lifespan, increased exploratory and decreased anxiety-based behaviors, which are characteristic behavioral changes under CR. Moreover, *Gipr*^{-/-} mice showed increased Sirt1 and Nampt expression in the adipose tissue. GIP suppressed α -lipoic acid-induced Sirt1 expression and activity in differentiated adipocytes.

CONCLUSIONS: Although maintenance of CR is difficult, food intake and muscle endurance of *Gipr*^{-/-} mice were similar to those of wild-type mice. Inhibition of GIP signaling may be a novel strategy to extend the lifespan of diabetic patients.

A farnesyltransferase inhibitor activates lysosomes and reduces tau pathology in mice with tauopathy

Tau inclusions are a shared feature of many neurodegenerative diseases, among them frontotemporal dementia caused by tau mutations. Treatment approaches for these conditions include targeting posttranslational modifications of tau proteins, maintaining a steady-state amount of tau, and preventing its tendency to aggregate. We discovered a new regulatory pathway for tau degradation that operates through the farnesylated protein, Rhes, a GTPase in the Ras family. Here, we show that treatment with the farnesyltransferase inhibitor lonafarnib reduced Rhes and decreased brain atrophy, tau inclusions, tau sumoylation, and tau ubiquitination in the rTg4510 mouse model of tauopathy. In addition, lonafarnib treatment attenuated behavioral abnormalities in rTg4510 mice and reduced microgliosis in mouse brain. Direct reduction of Rhes in the rTg4510 mouse by siRNA reproduced the results observed with lonafarnib treatment. The mechanism of lonafarnib action mediated by Rhes to reduce tau pathology was shown to operate through activation of lysosomes. We finally showed in mouse brain and in human induced pluripotent stem cell–derived neurons a normal developmental increase in Rhes that was initially suppressed by tau mutations. The known safety of lonafarnib revealed in human clinical trials for cancer suggests that this drug could be repurposed for treating tauopathies.

Nitration and Glycation Diminish the α -Synuclein Role in the Formation and Scavenging of Cu^{2+} -Catalyzed Reactive Oxygen Species

Humberto Martínez-Orozco[†], Laura Mariño[†], Ana Belén Uceda[†], Joaquin Ortega-Castro , Bartolomé Vilanova, Juan Frau, and Miquel Adrover* 

Human α -synuclein is a small monomeric protein (140 residues) essential to maintain the function of the dopaminergic neurons and the neuronal redox balance. However, it holds a dark side since it is able to clump inside the neurons forming insoluble aggregates known as Lewy bodies, which are considered the hallmark of Parkinson's disease. Sporadic mutations and nonenzymatic post-translational modifications are well-known to stimulate the formation of Lewy bodies. Yet, the effect of nonenzymatic post-translational modifications on the function of α -synuclein has been studied less intense. Therefore, here we study how nitration and glycation mediated by methylglyoxal affect the redox features of α -synuclein. Both diminish the ability of α -synuclein to chelate Cu^{2+} , except when N^{ϵ} -(carboxyethyl)lysine or N^{ϵ} -(carboxymethyl)lysine (two advanced glycation end products highly prevalent *in vivo*) are formed. This results in a lower capacity to prevent the Cu-catalyzed ascorbic acid degradation and to delay the formation of H_2O_2 . However, only methylglyoxal was able to abolish the ability of α -synuclein to inhibit the free radical release. Both nitration and glycation enhanced the α -synuclein availability to be damaged by $\text{O}_2^{\bullet-}$, although glycation made α -synuclein less reactive toward HO^{\bullet} . Our data represent the first report describing how nonenzymatic post-translational modifications might affect the redox function of α -synuclein, thus contributing to a better understanding of its pathological implications.

Cell Rep. 2019 Apr 23;27(4):1018-1026.e4. doi: 10.1016/j.celrep.2019.03.096.

Regional Molecular Mapping of Primate Synapses during Normal Healthy Aging.

[Graham LC](#)¹, [Naldrett MJ](#)², [Kohama SG](#)³, [Smith C](#)⁴, [Lamont DJ](#)⁵, [McColl BW](#)⁶, [Gillingwater TH](#)⁴, [Skehel P](#)⁷, [Urbanski HF](#)³, [Wishart TM](#)⁸.

Author information

Abstract

Normal mammalian brain aging is characterized by the selective loss of discrete populations of dendritic spines and synapses, particularly affecting neuroanatomical regions such as the hippocampus. Although previous investigations have quantified this morphologically, the molecular pathways orchestrating preferential synaptic vulnerability remain to be elucidated. Using quantitative proteomics and healthy rhesus macaque and human patient brain regional tissues, we have comprehensively profiled the temporal expression of the synaptic proteome throughout the adult lifespan in differentially vulnerable brain regions. Comparative profiling of hippocampal (age vulnerable) and occipital cortex (age resistant) synapses revealed discrete and dynamic alterations in the synaptic proteome, which appear unequivocally conserved between species. The generation of these unique and important datasets will aid in delineating the molecular mechanisms underpinning primate brain aging, in addition to deciphering the regulatory biochemical cascades governing neurodegenerative disease pathogenesis.

[Cell Rep.](#) 2019 Apr 23;27(4):1293-1306.e6. doi: 10.1016/j.celrep.2019.03.099.

The Major Risk Factors for Alzheimer's Disease: Age, Sex, and Genes Modulate the Microglia Response to A β Plaques.

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⊕ Author information

Abstract

Gene expression profiles of more than 10,000 individual microglial cells isolated from cortex and hippocampus of male and female App^{NL-G-F} mice over time demonstrate that progressive amyloid- β accumulation accelerates two main activated microglia states that are also present during normal aging. Activated response microglia (ARMs) are composed of specialized subgroups overexpressing MHC type II and putative tissue repair genes (*Dkk2*, *Gpnmb*, and *Spp1*) and are strongly enriched with Alzheimer's disease (AD) risk genes. Microglia from female mice progress faster in this activation trajectory. Similar activated states are also found in a second AD model and in human brain. *Apoe*, the major genetic risk factor for AD, regulates the ARMs but not the interferon response microglia (IRMs). Thus, the ARMs response is the converging point for aging, sex, and genetic AD risk factors.

The neural stem cell (NSC) reservoir can be harnessed for stem cell-based regenerative therapies. Zebrafish remarkably regenerate their brain by inducing NSC plasticity in a Amyloid- β -42 ($A\beta$ 42)-induced experimental Alzheimer's disease (AD) model. Interleukin-4 (IL-4) is also critical for AD-induced NSC proliferation. However, the mechanisms of this response have remained unknown. Using single-cell transcriptomics in the adult zebrafish brain, we identify distinct subtypes of NSCs and neurons and differentially regulated pathways and their gene ontologies and investigate how cell-cell communication is altered through ligand-receptor pairs in AD conditions. Our results propose the existence of heterogeneous and spatially organized stem cell populations that react distinctly to amyloid toxicity. This resource article provides an extensive database for the molecular basis of NSC plasticity in the AD model of the adult zebrafish brain. Further analyses of stem cell heterogeneity and neuro-regenerative ability at single-cell resolution could yield drug targets for mobilizing NSCs for endogenous neuro-regeneration in humans.

[Aging \(Albany NY\)](#), 2019 Apr 19. doi: 10.18632/aging.101912. [Epub ahead of print]

The widespread increase in inter-individual variability of gene expression in the human brain with age.

[Kedlian VR](#)^{#1,2}, [Donertas HM](#)^{#1}, [Thornton JM](#)¹.

⊕ Author information

Abstract

Aging is broadly defined as a time-dependent progressive decline in the functional and physiological integrity of organisms. Previous studies and evolutionary theories of aging suggest that aging is not a programmed process but reflects dynamic stochastic events. In this study, we test whether transcriptional noise shows an increase with age, which would be expected from stochastic theories. Using human brain transcriptome dataset, we analyzed the heterogeneity in the transcriptome for individual genes and functional pathways, employing different analysis methods and pre-processing steps. We show that unlike expression level changes, changes in heterogeneity are highly dependent on the methodology and the underlying assumptions. Although the particular set of genes that can be characterized as differentially variable is highly dependent on the methods, we observe a consistent increase in heterogeneity at every level, independent of the method. In particular, we demonstrate a weak but reproducible transcriptome-wide shift towards an increase in heterogeneity, with twice as many genes significantly increasing as opposed to decreasing their heterogeneity. Furthermore, this pattern of increasing heterogeneity is not specific but is associated with a wide range of pathways.

Metformin and Reduced Risk of Cancer in the Hong Kong Diabetes Registry: Real Effect or Immortal Time Bias?

Zhang ZJ¹.

⊕ Author information

Abstract

BACKGROUND: Whether metformin reduces cancer risk has been hotly debated. One common opinion is that the observed beneficial effects of metformin are the consequence of immortal time bias.

OBJECTIVE: To examine whether the observed beneficial effects of metformin on cancer risk are the consequence of immortal time bias.

DESIGN: Retrospective cohort study.

PARTICIPANTS: A cohort of 3485 patients who started metformin before or at enrollment, 1226 patients who initiated metformin after enrollment, and an unexposed group of 1392 patients who never used metformin.

MAIN MEASURES: Metformin users were categorized into 11 groups in terms of length of time between metformin initiation and enrollment. The percent changes in immortal person-time were calculated for each group.

RESULTS: As the groups of current metformin users ($n = 3485$) were added sequentially to the metformin group with potential immortal time bias ($n = 1226$), the proportion of immortal person-time decreased gradually by 74%. As the immortal time decreased, the association between metformin and cancer risk remained statistically significant (uncorrected hazard ratio 0.54, 95% confidence interval 0.42-0.69, $P < 0.0001$).

CONCLUSION: The change in the association between metformin and cancer is small compared with the changes in the proportion of immortal time, suggesting that immortal time bias does not account for the observed beneficial effect of metformin on cancer risk. Further studies are warranted to confirm this finding in other cohort studies.

Transcriptomics-Based Screening Identifies Pharmacological Inhibition of Hsp90 as a Means to Defer Aging

Aging strongly influences human morbidity and mortality. Thus, aging-preventive compounds could greatly improve our health and lifespan. Here we screened for such compounds, known as geroprotectors, employing the power of transcriptomics to predict biological age. Using age-stratified human tissue transcriptomes and machine learning, we generated age classifiers and applied these to transcriptomic changes induced by 1,309 different compounds in human cells, ranking these compounds by their ability to induce a “youthful” transcriptional state. Testing the top candidates in *C. elegans*, we identified two Hsp90 inhibitors, monorden and tanespimycin, which extended the animals’ lifespan and improved their health. Hsp90 inhibition induces expression of heat shock proteins known to improve protein homeostasis. Consistently, monorden treatment improved the survival of *C. elegans* under proteotoxic stress, and its benefits depended on the cytosolic unfolded protein response-inducing transcription factor HSF-1. Taken together, our method represents an innovative geroprotector screening approach and was able to identify a class that acts by improving protein homeostasis.

Analysis of the coding sequences of clownfish reveals molecular convergence in the evolution of lifespan

Background

Standard evolutionary theories of aging postulate that reduced extrinsic mortality leads to evolution of longevity. Clownfishes of the genus *Amphiprion* live in a symbiotic relationship with sea anemones that provide protection from predators. We performed a survey and identified at least two species with a lifespan of over 20 years. Given their small size and ease of captive reproduction, clownfish lend themselves as experimental models of exceptional longevity. To identify genetic correlates of exceptional longevity, we sequenced the transcriptomes of *Amphiprion percula* and *A. clarkii* and performed a scan for positively-selected genes (PSGs).

Results

The PSGs that we identified in the last common clownfish ancestor were compared with PSGs detected in long-lived mole rats and short-lived killifishes revealing convergent evolution in processes such as mitochondrial biogenesis. Among individual genes, the Mitochondrial Transcription Termination Factor 1 (*MTERF1*), was positively-selected in all three clades, whereas the Glutathione S-Transferase Kappa 1 (*GSTK1*) was under positive selection in two independent clades. For the latter, homology modelling strongly suggested that positive selection targeted enzymatically important residues.

Conclusions

These results indicate that specific pathways were recruited in independent lineages evolving an exceptionally extended or shortened lifespan and point to mito-nuclear balance as a key factor.

Genetic identification and characterization of three genes that prevent accumulation of oxidative DNA damage in *Drosophila* adult tissues.

[Okumura K¹](#), [Nishihara S¹](#), [Inoue YH²](#).

⊕ Author information

Abstract

Reactive oxygen species generated in the process of energy production represent a major cause of oxidative DNA damage. Production of the oxidized guanine base, 8-oxo-guanine (8-oxoG), results in mismatched pairing with adenine and subsequently leads to G:C to T:A transversions after DNA replication. Our previous study demonstrated that *Drosophila* CG1795 encodes an ortholog of Ogg1, which is essential for the elimination of 8-oxoG. Moreover, the *Drosophila* ribosomal protein S3 (RpS3) possesses N-glycosylase activity that eliminates 8-oxoG *in vitro*. In this study, we show that RpS3 heterozygotes hyper-accumulate 8-oxoG in midgut cell nuclei after oxidant feeding, suggesting that RpS3 is required for the elimination of 8-oxoG in *Drosophila* adults. We further showed that several muscle-aging phenotypes were significantly accelerated in RpS3 heterozygotes. Ogg1 is localized in the nucleus, while RpS3 is in the cytoplasm, closely associated with endoplasmic reticulum networks. Results of genetic analyses also suggest that these two proteins operate similarly but independently in the elimination of oxidized guanine bases from genomic DNA. Next, we obtained genetic evidence suggesting that CG42813 functions as the *Drosophila* ortholog of mammalian Mth1 in the elimination of oxidized dGTP (8-oxo-dGTP) from the nucleotide pool. Depletion of this gene significantly increased the number of DNA damage foci in the nuclei of *Drosophila* midgut cells. Furthermore, several aging-related phenotypes such as age-dependent loss of adult locomotor activities and accumulation of polyubiquitylated proteins in adult muscles were also significantly accelerated in CG42813-depleted flies. Lastly, we investigated the phenotype of adults depleted of CG9272, which encodes a protein with homology to mammalian Nth1 that is essential for the elimination of oxidized thymine. Excessive accumulation of oxidized bases was observed in the epithelial cell nuclei after oxidant feeding. In conclusion, three genes that prevent accumulation of oxidative DNA damage were identified in *Drosophila*.

[Elife](#). 2019 May 3;8. pii: e43059. doi: 10.7554/eLife.43059. [Epub ahead of print]

Intrinsically aggregation-prone proteins form amyloid-like aggregates and contribute to tissue aging in *C. elegans*.

[Huang C](#)¹, [Wagner-Valladolid S](#)², [Stephens AD](#)², [Jung R](#)¹, [Poudel C](#)², [Sinnige T](#)³, [Lechler MC](#)¹, [Schlörfl N](#)¹, [Lu M](#)², [Laine RF](#)², [Michel CH](#)², [Vendruscolo M](#)³, [Kaminski CF](#)², [Kaminski Schierle GS](#)², [David DC](#)¹.

⊕ Author information

Abstract

Reduced protein homeostasis leading to increased protein instability is a common molecular feature of aging, but it remains unclear whether this is a cause or consequence of the aging process. In neurodegenerative diseases and other amyloidoses, specific proteins self-assemble into amyloid fibrils and accumulate as pathological aggregates in different tissues. More recently, widespread protein aggregation has been described during normal aging. Until now, an extensive characterization of the nature of age-dependent protein aggregation has been lacking. Here, we show that age-dependent aggregates are rapidly formed by newly synthesized proteins and have an amyloid-like structure resembling that of protein aggregates observed in disease. We then demonstrate that age-dependent protein aggregation accelerates the functional decline of different tissues in *C. elegans*. Together, these findings imply that amyloid-like aggregates contribute to the aging process and therefore could be important targets for strategies designed to maintain physiological functions in the late stages of life.

PLoS One. 2019 Apr 12;14(4):e0214523. doi: 10.1371/journal.pone.0214523. eCollection 2019.

Integration of heterogeneous functional genomics data in gerontology research to find genes and pathway underlying aging across species.

Bubier JA¹, Sutphin GL², Reynolds TJ³, Korstanje R⁴, Fuksman-Kumpa A¹, Baker EJ³, Langston MA⁵, Chesler EJ^{1,4}.

⊕ Author information

Abstract

Understanding the biological mechanisms behind aging, lifespan and healthspan is becoming increasingly important as the proportion of the world's population over the age of 65 grows, along with the cost and complexity of their care. BigData oriented approaches and analysis methods enable current and future bio-gerontologists to synthesize, distill and interpret vast, heterogeneous data from functional genomics studies of aging. GeneWeaver is an analysis system for integration of data that allows investigators to store, search, and analyze immense amounts of data including user-submitted experimental data, data from primary publications, and data in other databases. Aging related genome-wide gene sets from primary publications were curated into this system in concert with data from other model-organism and aging-specific databases, and applied to several questions in gerontology using. For example, we identified Cd63 as a frequently represented gene among aging-related genome-wide results. To evaluate the role of Cd63 in aging, we performed RNAi knockdown of the *C. elegans* ortholog, *tsp-7*, demonstrating that this manipulation is capable of extending lifespan. The tools in GeneWeaver enable aging researchers to make new discoveries into the associations between the genes, normal biological processes, and diseases that affect aging, healthspan, and lifespan.

Untangling Aging Using Dynamic, Organism-Level Phenotypic Networks

Research on aging requires the ability to measure aging, and therein lies a challenge: it is impossible to measure every molecular, cellular, and physiological change that develops over time, but it is difficult to prioritize phenotypes for measurement because it is unclear which biological changes should be considered aspects of aging and, further, which species and environments exhibit “real aging.” Here, I propose a strategy to address this challenge: rather than classify phenotypes as “real aging” or not, conceptualize aging as the set of all age-dependent phenotypes and appreciate that this set and its underlying mechanisms may vary by population. Use automated phenotyping technologies to measure as many age-dependent phenotypes as possible within individuals over time, prioritizing organism-level (i.e., physiological) phenotypes in order to enrich for health relevance. Use those high-dimensional phenotypic data to construct dynamic networks that allow aging to be studied with unprecedented sophistication and rigor.

REVIEWS/COMMENTS/
METHODS/EDITORIALS

[J Gerontol A Biol Sci Med Sci](#). 2019 Apr 17. pii: glz098. doi: 10.1093/gerona/glz098. [Epub ahead of print]

Inconvenient Truths About Human Longevity.

[Olshansky SJ](#)¹, [Carnes BA](#)².

⊕ Author information

Abstract

The rise in human longevity is one of humanity's crowning achievements. While advances in public health beginning in the 19th century initiated the rise in life expectancy, recent gains have been achieved by reducing death rates at middle and older ages. A debate about the future course of life expectancy has been ongoing for the last quarter century. Some suggest that historical trends in longevity will continue and radical life extension is either visible on the near horizon or it has already arrived; while others suggest there are biologically based limits to duration of life, and those limits are being approached now. In "inconvenient truths about human longevity" we lay out the line of reasoning and evidence for why there are limits to human longevity; why predictions of radical life extension are unlikely to be forthcoming; why health extension should supplant life extension as the primary goal of medicine and public health; and why promoting advances in aging biology may allow humanity to break through biological barriers that influence both lifespan and healthspan, allowing for a welcome extension of the period of healthy life, a compression of morbidity, but only a marginal further increase in life expectancy.

“The approximately 4600 genetic counselors in the United States represent an increase of almost 50% since 2014 (5). Over the past year, 14 new master's programs (including 1 at Columbia University) were accredited, bringing the total to 45.”

EDITORIALS | 30 APRIL 2019

Precision Medicine for Clinicians: The Future Begins Now

Lee Goldman, MD, MPH; Jill S. Goldman, MS, MPhil

[Article, Author, and Disclosure Information](#)


FULL TEXT



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Until late in the 20th century, medical practice was largely based on case reports and a physician's personal experience, hopefully guided by the underlying pathophysiology. Practice patterns were heavily influenced by the logic and biases of a respected local “guru,” whose therapeutic theology, though admired at the home institution, might be heresy to another institution's competing guru.

Telomeres and telomerase: three decades of progress

Jerry W. Shay  & Woodring E. Wright

Many recent advances have emerged in the telomere and telomerase fields. This Timeline article highlights the key advances that have expanded our views on the mechanistic underpinnings of telomeres and telomerase and their roles in ageing and disease. Three decades ago, the classic view was that telomeres protected the natural ends of linear chromosomes and that telomerase was a specific telomere-terminal transferase necessary for the replication of chromosome ends in single-celled organisms. While this concept is still correct, many diverse fields associated with telomeres and telomerase have substantially matured. These areas include the discovery of most of the key molecular components of telomerase, implications for limits to cellular replication, identification and characterization of human genetic disorders that result in premature telomere shortening, the concept that inhibiting telomerase might be a successful therapeutic strategy and roles for telomeres in regulating gene expression. We discuss progress in these areas and conclude with challenges and unanswered questions in the field.

Iron and redox cycling. Do's and don'ts

W.H. Koppenol ^{a, b}  , R.H. Hider ^c

A major form of toxicity arises from the ability of iron to **redox cycle**, that is, to accept an electron from a reducing compound and to pass it on to H_2O_2 (the **Fenton reaction**). In order to do so, iron must be suitably complexed to avoid formation of Fe_2O_3 . The ligands determine the electrode potential; this information should be known before experiments are carried out. Only one-electron transfer reactions are likely to be significant; thus two-electron potentials should not be used to determine whether an iron(III) complex can be reduced or oxidized. Ascorbate is the relevant **reducing agent** in blood serum, which means that **iron toxicity** in this compartment arises from the ascorbate-driven Fenton reaction. In the **cytosol**, an iron(II)-glutathione complex is likely to be the low-molecular weight **iron complex** involved in toxicity. When physiologically relevant concentrations are used the window of redox opportunity ranges from +0.1 V to +0.9 V. The electrode potential for non-transferrin-bound iron in the form of iron **citrate** is close to 0 V and the reduction of iron(III) citrate by ascorbate is slow. The clinically utilised **chelators** **desferrioxamine**, **deferiprone** and **deferasirox** in each case render iron complexes with large negative electrode potentials, thus being effective in preventing iron redox cycling and the associated toxicity resulting from such activity. There is still uncertainty about the product of the Fenton reaction, HO^\bullet or FeO^{2+} .

Applications of machine learning in drug discovery and development

Jessica Vamathevan , Dominic Clark, Paul Czodrowski, Ian Dunham, Edgardo Ferran, George Lee, Bin Li, Anant Madabhushi, Parantu Shah, Michaela Spitzer & Shanrong Zhao

Drug discovery and development pipelines are long, complex and depend on numerous factors. Machine learning (ML) approaches provide a set of tools that can improve discovery and decision making for well-specified questions with abundant, high-quality data. Opportunities to apply ML occur in all stages of drug discovery. Examples include target validation, identification of prognostic biomarkers and analysis of digital pathology data in clinical trials. Applications have ranged in context and methodology, with some approaches yielding accurate predictions and insights. The challenges of applying ML lie primarily with the lack of interpretability and repeatability of ML-generated results, which may limit their application. In all areas, systematic and comprehensive high-dimensional data still need to be generated. With ongoing efforts to tackle these issues, as well as increasing awareness of the factors needed to validate ML approaches, the application of ML can promote data-driven decision making and has the potential to speed up the process and reduce failure rates in drug discovery and development.

[Biogerontology](#), 2019 Feb 23. doi: 10.1007/s10522-019-09802-9. [Epub ahead of print]

The mTORC1-autophagy pathway is a target for senescent cell elimination.

[Kucheryavenko O](#)^{1,2}, [Nelson G](#)¹, [von Zglinicki T](#)³, [Korolchuk V](#)⁴, [Carroll B](#)⁵.

⊕ Author information


Abstract

Cellular senescence has recently been established as a key driver of organismal ageing. The state of senescence is controlled by extensive rewiring of signalling pathways, at the heart of which lies the mammalian Target of Rapamycin Complex I (mTORC1). Here we discuss recent publications aiming to establish the mechanisms by which mTORC1 drives the senescence program. In particular, we highlight our data indicating that mTORC1 can be used as a target for senescence cell elimination in vitro. Suppression of mTORC1 is known to extend lifespan of yeast, worms, flies and some mouse models and our proof-of-concept experiments suggest that it can also act by reducing senescent cell load in vivo.

[Nutrition](#). 2019 Feb 26;65:33-38. doi: 10.1016/j.nut.2019.01.020. [Epub ahead of print]

In search of nutritional anti-aging targets: TOR inhibitors, SASP modulators, and BCL-2 family suppressors.

[Sharma R](#)¹, [Padwad Y](#)².

 **Author information**

Abstract

In pursuit of developing anti-aging or age-delaying strategies, nutritional interventions have long been considered promising candidates. However, emerging advances in the understanding of the causes and effects of senescence per se have enhanced the prospects of a more focused approach in the exploration of therapies aimed at the modulation of aging. The aim of this study was to review recent developments on the molecular basis of aging and provide evidence that regulation of the mechanistic target of rapamycin (mTOR), senescence-associated secretory phenotype (SASP), and apoptotic pathways could be the key mechanistic targets of prospective senescence modulatory interventions. The emerging role of nutraceuticals in specifically targeting these molecular aspects of senescence are reviewed with the rationale of identifying novel opportunities and challenges in formulating food- and nutrition-based anti-aging therapies.

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The interface of aging and the circadian clock

Jesse Britz, Shelley A. Tischkau  

The **circadian clock** drives a number of internal processes and relies primarily on external environmental cues to align the master clock in the **suprachiasmatic nucleus**, responsible for temporal synchronization of peripheral oscillators in various **organ systems**. This review examines recent evidence for a bidirectional relationship between aging and the circadian system. Recent evidence shows that the aging process can have a direct influence on how the circadian network responds to external stimuli, including altered responsiveness of both central and peripheral oscillators to light stimuli or to changes in the **light/dark cycle**. Conversely, chronic irregular light/dark exposure can be a detriment to health downstream of the circadian network. Interactions between aging and circadian regulation of cognition, **Alzheimer's disease**, and metabolism are discussed.

The new genetic landscape of Alzheimer's disease: from amyloid cascade to genetically driven synaptic failure hypothesis?


[Dourlen P](#)¹, [Kilinc D](#)¹, [Malmanche N](#)¹, [Chapuis J](#)¹, [Lambert JC](#)².

⊕ Author information

Abstract

A strong genetic predisposition (60-80% of attributable risk) is present in Alzheimer's disease (AD). In view of this major genetic component, identification of the genetic risk factors has been a major objective in the AD field with the ultimate aim to better understand the pathological processes. In this review, we present how the genetic risk factors are involved in APP metabolism, β -amyloid peptide production, degradation, aggregation and toxicity, innate immunity, and Tau toxicity. In addition, on the basis of the new genetic landscape, resulting from the recent high-throughput genomic approaches and emerging neurobiological information, we propose an over-arching model in which the focal adhesion pathway and the related cell signalling are key elements in AD pathogenesis. The core of the focal adhesion pathway links the physiological functions of amyloid precursor protein and Tau with the pathophysiological processes they are involved in. This model includes several entry points, fitting with the different origins for the disease, and supports the notion that dysregulation of synaptic plasticity is a central node in AD. Notably, our interpretation of the latest data from genome wide association studies complements other hypotheses already developed in the AD field, i.e., amyloid cascade, cellular phase or propagation hypotheses. Genetically driven synaptic failure hypothesis will need to be further tested experimentally within the general AD framework.

Impact of advanced glycation end products (AGEs) signaling in coronary artery disease

Marinos Kosmopoulos, Dimitrios Drekolias, Phaedon D. Zavras, Christina Piperi  , Athanasios G. Papavassiliou

Coronary artery disease remains the leading cause of mortality in adult diabetic population with however, a high predominance also in non-diabetic subjects. In search of common molecular mechanisms and metabolic by-products with potential pathogenic role, increased advanced glycation end products (AGEs) present a critical biomarker for CAD development in both cases. Interaction of AGEs with their transmembrane cell receptor, RAGE in endothelial and smooth muscle cells as well as in platelets, activates intracellular signaling that leads to endothelial injury, modulation of vascular smooth muscle cell function and altered platelet activity. Furthermore, tissue accumulation of AGEs affects current treatment approaches being involved in stent restenosis. The present review provides an update of AGE-induced molecular mechanisms involved in CAD pathophysiology while it discusses emerging therapeutic interventions targeting AGE reduction and AGE-RAGE signaling with beneficial clinical outcome.

[Mech Ageing Dev.](#) 2019 Mar 26;180:42-48. doi: 10.1016/j.mad.2019.03.005. [Epub ahead of print]

Frailty index as a biomarker of lifespan and healthspan: Focus on pharmacological interventions.

[Palliyaguru DL](#)¹, [Moats JM](#)¹, [Di Germanio C](#)¹, [Bernier M](#)¹, [de Cabo R](#)².


⊕ Author information

Abstract

Although survival has been the focus of aging research for many years, the field is rapidly evolving towards incorporating healthspan and health indices in studies that explore aging-related outcomes. Frailty is one such measure that is tightly correlated with human aging. Several frailty measures have been developed that focus on phenotypes of aging, including physical, cognitive and metabolic health that define healthspan. The extent at which cumulative deficits associated with frailty predict functional characteristics of healthy aging and longevity is currently unknown. A growing consensus for the use of animal models has emerged to evaluate a composite measure of frailty that provides a translational basis to understanding human frailty. In this review, we will focus on the impact of several anti-aging interventions, some of which have been characterized as caloric restriction (CR) mimetics such as metformin, rapamycin, and resveratrol as well as more novel approaches that are emerging in the field - nicotinamide adenine dinucleotide precursors, small molecule activators of sirtuins, and senolytics - on a number of frailty measurements associated with aging-related outcomes in mice and discuss the translatability of such measures to human frailty.

OTHER RESEARCH

Multiplexed detection of proteins, transcriptomes, clonotypes and CRISPR perturbations in single cells

Eleni P. Mimitou, Anthony Cheng, Antonino Montalbano, Stephanie Hao, Marlon Stoeckius, Mateusz Legut, Timothy Roush, Alberto Herrera, Efthymia Papalexi, Zhengqing Ouyang, Rahul Satija, Neville E. Sanjana, Sergei B. Koralov & Peter Smibert 

Multimodal single-cell assays provide high-resolution snapshots of complex cell populations, but are mostly limited to transcriptome plus an additional modality. Here, we describe expanded CRISPR-compatible cellular indexing of transcriptomes and epitopes by sequencing (ECCITE-seq) for the high-throughput characterization of at least five modalities of information from each single cell. We demonstrate application of ECCITE-seq to multimodal CRISPR screens with robust direct single-guide RNA capture and to clonotype-aware multimodal phenotyping of cancer samples.

Predicting protein structure from sequence is a central challenge of biochemistry. Co-evolution methods show promise, but an explicit sequence-to-structure map remains elusive. Advances in deep learning that replace complex, human-designed pipelines with differentiable models optimized end to end suggest the potential benefits of similarly reformulating structure prediction. Here, we introduce an end-to-end differentiable model for protein structure learning. The model couples local and global protein structure via geometric units that optimize global geometry without violating local covalent chemistry. We test our model using two challenging tasks: predicting novel folds without co-evolutionary data and predicting known folds without structural templates. In the first task, the model achieves state-of-the-art accuracy, and in the second, it comes within 1–2 Å; competing methods using co-evolution and experimental templates have been refined over many years, and it is likely that the differentiable approach has substantial room for further improvement, with applications ranging from drug discovery to protein design.

Restoration of brain circulation and cellular functions hours post-mortem

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The brains of humans and other mammals are highly vulnerable to interruptions in blood flow and decreases in oxygen levels. Here we describe the restoration and maintenance of microcirculation and molecular and cellular functions of the intact pig brain under ex vivo normothermic conditions up to four hours post-mortem. We have developed an extracorporeal pulsatile-perfusion system and a haemoglobin-based, acellular, non-coagulative, echogenic, and cytoprotective perfusate that promotes recovery from anoxia, reduces reperfusion injury, prevents oedema, and metabolically supports the energy requirements of the brain. With this system, we observed preservation of cytoarchitecture; attenuation of cell death; and restoration of vascular dilatory and glial inflammatory responses, spontaneous synaptic activity, and active cerebral metabolism in the absence of global electrocorticographic activity. These findings demonstrate that under appropriate conditions the isolated, intact large mammalian brain possesses an underappreciated capacity for restoration of microcirculation and molecular and cellular activity after a prolonged post-mortem interval.

The NASA Twins Study: A multidimensional analysis of a year-long human spaceflight

RESULTS

Physiological, telomeric, transcriptomic, epigenetic, proteomic, metabolomic, immune, microbiomic, cardiovascular, vision-related, and cognitive data were collected over 25 months. Some biological functions were not significantly affected by spaceflight, including the immune response (T cell receptor repertoire) to the first test of a vaccination in flight. However, significant changes in multiple data types were observed in association with the spaceflight period; the majority of these eventually returned to a preflight state within the time period of the study. These included changes in telomere length, gene regulation measured in both epigenetic and transcriptional data, gut microbiome composition, body weight, carotid artery dimensions, subfoveal choroidal thickness and peripapillary total retinal thickness, and serum metabolites. In addition, some factors were significantly affected by the stress of returning to Earth, including inflammation cytokines and immune response gene networks, as well as cognitive performance. For a few measures, persistent changes were observed even after 6 months on Earth, including some genes' expression levels, increased DNA damage from chromosomal inversions, increased numbers of short telomeres, and attenuated cognitive function.

CONCLUSION

Given that the majority of the biological and human health variables remained stable, or returned to baseline, after a 340-day space mission, these data suggest that human health can be mostly sustained over this duration of spaceflight. The persistence of the molecular changes (e.g., gene expression) and the extrapolation of the identified risk factors for longer missions (>1 year) remain estimates and should be demonstrated with these measures in future astronauts. Finally, changes described in this study highlight pathways and mechanisms that may be vulnerable to spaceflight and may require safeguards for longer space missions; thus, they serve as a guide for targeted countermeasures or monitoring during future missions.