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Scientific News
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Sven Bulterijs

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Fourth Eurosymposium on Healthy Ageing

We envision a world free of age-related diseases

November 8-10, 2018
Muntpunt, Brussels (Belgium)

Speakers:

- Thomas von Zglinicki
- Marco Demaria
- Andrea Ablasser
- Peter de Keizer
- Björn Schumacher
- Guido Kroemer
- Georg Füllen
- Andrea Maier
- Aubrey de Grey
- Alexey Moskalev
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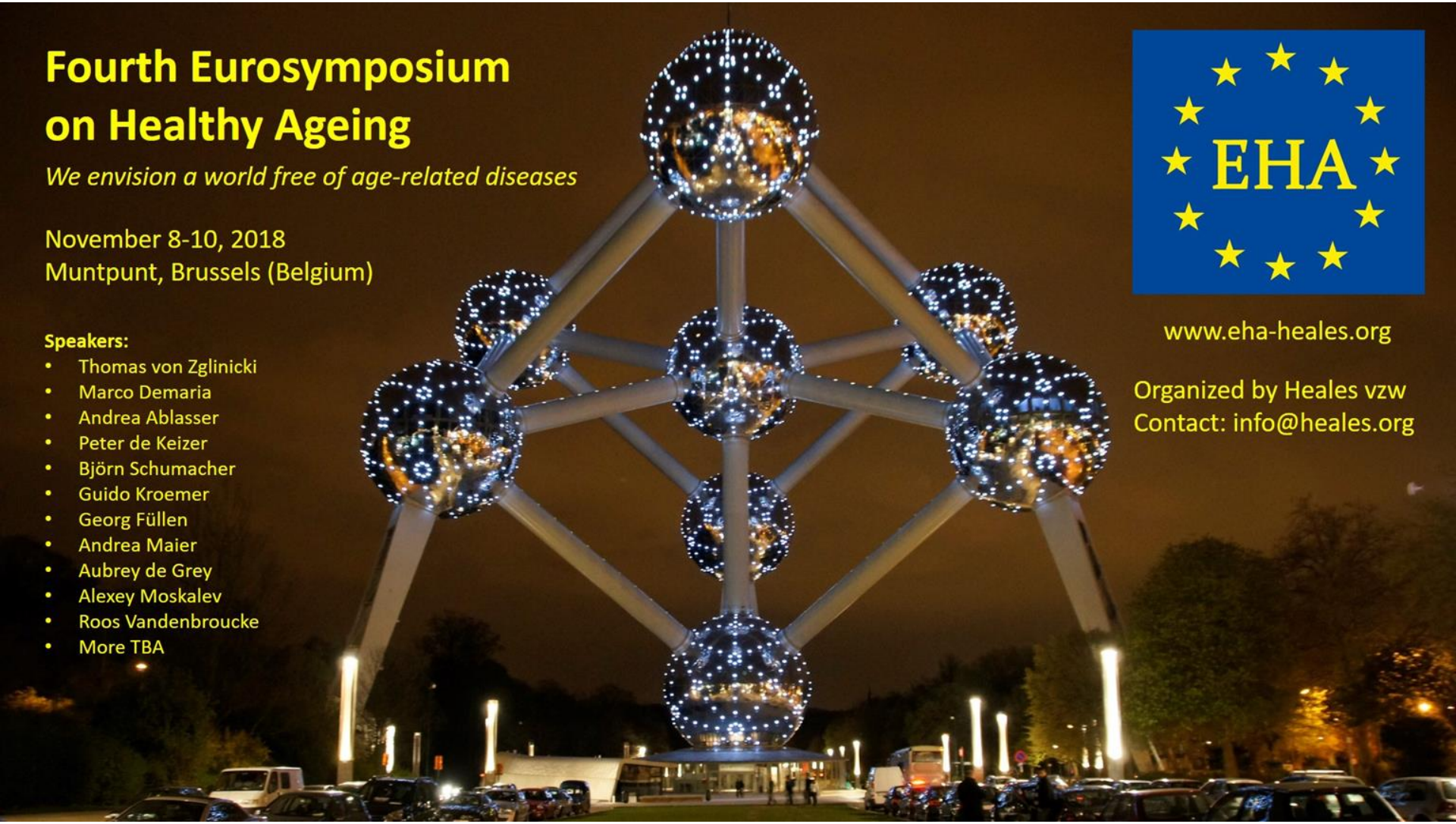
- More TBA



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Opening the door to treating ageing as a disease

Death in old age was historically attributed to just that—ie, old age and natural causes. However, with increasing life expectancy and the desire to maintain good health in older age for as long as possible (so-called healthy ageing), calls to recognise ageing as a disease that can be treated are increasingly relevant and debated, despite the lack of a universally accepted set of ageing biomarkers and uncertainty about the time of transition to disease.

Progress in being able to classify, and thus treat, ageing as a disease was made recently when WHO implemented an extension code for 'Ageing-related' (XT9T) diseases—defined as those "caused by pathological processes which persistently lead to the loss of organism's adaptation and progress in older ages"—in the latest version of the International Classification of Diseases, ICD-11. The new code, implemented as a result of a joint proposal submitted to WHO's ICD-11 Task Force by researchers from the Biogerontology Research Foundation, the International Longevity Alliance, and the Council for Public Health and the Problems of Demography, can be immediately applied to relevant conditions listed in ICD-11 as well as to newly recognised conditions in the future. As ICD codes are prerequisite for the registration of all new drugs and therapies, the recognition of age as a pathological process, together with replacement of the ICD-10 'Senility' (R54) code with 'Old age' (MG2A) in ICD-11, represents undeniable progress towards overcoming the regulatory obstacles that have thus far hampered the development of therapeutic interventions and preventative strategies targeting ageing and age-related diseases.

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Citi Lists Anti-Aging Medicines in Top 10 Disruptive Technologies

Steve Hill August 30, 2018 0

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AgeX Therapeutics Acquires Technology to Regulate Immune Tolerance

Technology supports Company's strategy for off-the-shelf (allogeneic) cell-based regenerative medicine products through the use of the HLA-G gene

August 16, 2018 08:00 AM Eastern Daylight Time

ALAMEDA, Calif.--(BUSINESS WIRE)--AgeX Therapeutics, Inc., a subsidiary of BioTime, Inc. (NYSE American: BTX), focused on the development and commercialization of novel therapeutics targeting human aging, today announced that it has acquired certain patents and patent applications from Escape Therapeutics relating primarily to the use of the *HLA-G* gene to suppress rejection of transplanted cells and tissues. The Company plans to utilize the technology in conjunction with its pluripotent stem cell platform for applications in regenerative medicine.

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10 AUG 2018

Repair Biotechnologies Closes Seed Round, Joins Grapeseed.bio Incubator

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I had promised a short update on progress at Repair Biotechnologies, the company that Bill Cherman and I founded earlier this year to help advance the state of therapies to treat aging, and here it is. We recently closed a seed round with a number of investors in our close-knit community, and are presently setting up our modest headquarters near Syracuse, NY, alongside our allies at Ichor Therapeutics. The staff at Ichor, fresh from a sizable investment made by Juvenescence in their subsidiary Antoxerene, have launched an incubator, Grapeseed.bio, to encourage the development of new companies focused on the treatment of aging. Repair Biotechnologies is the first such company to be accepted to the program.

Our initial development program at Repair Biotechnologies progresses, and I'm pleased to be able to say that we have made our first scientific hire. We were fortunate to near immediately connect with a very talented protein biochemist in Syracuse, who will be joining us later this month. We continue to interview in search of another entrepreneurial scientist, someone with a cell biology and gene therapy background. If you know of scientists with an interest in aging and the talent to make a difference, please do point them in our direction.

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Gene-silencing technology gets first drug approval after 20-year wait

The US Food and Drug Administration's decision breathes new life into RNA-interference therapies.

US regulators have approved the first therapy based on RNA interference (RNAi), a technique that can be used to silence specific genes linked to disease. The drug, patisiran, targets a rare condition that can impair heart and nerve function.

The approval, announced by the US Food and Drug Administration on 10 August, is a landmark for a field that has struggled for nearly two decades to prove its worth in the clinic. Researchers first discovered RNAi 20 years ago[1], sparking hopes of a revolutionary new approach to medicine. Since then, however, a series of setbacks has lessened those expectations.

"This approval is key for the RNAi field," says James Cardia, head of business development at RXi Pharmaceuticals in Marlborough, Massachusetts, which is developing RNAi treatments. "This is transformational."

Can Pension Funds Partially Manage Longevity Risk by Investing in a Longevity Megafund?

Edouard Debonneuil [1,†,*], Anne Eyraud-Loisel [1,†] and Frédéric Planchet [1,2,†]

Pension funds, which manage the financing of a large share of global retirement schemes, need to invest their assets in a diversified manner and over long durations while managing interest rate and longevity risks. In recent years, a new type of investment has emerged, that we call a longevity megafund, which invests in clinical trials for solutions against lifespan-limiting diseases and provides returns positively correlated with longevity. After describing ongoing biomedical developments against ageing-related diseases, we model the needed capital for pension funds to face longevity risk and find that it is far above current practices. After investigating the financial returns of pharmaceutical developments, we estimate the returns of a longevity megafund. Combined, our models indicate that investing in a longevity megafund is an appropriate method to significantly reduce longevity risk and the associated economic capital need. View Full-Text

Estimating the future health and aged care expenditure in Australia with changes in morbidity

Anthony Harris, Anurag Sharma

Aims

We estimate the pure effect of ageing on total health and aged care expenditure in Australia in the next 20 years.

Methods

We use a simple demographic projection model for the number of people in older age groups along with a needs based estimate of changes in the public and private cost of care per person in each group adjusted for expected changes in morbidity.

Results

A pure ageing model of expenditure growth predicts an increase in health expenditure per elderly person from $7439 in 2015 to $9594 in 2035 and an increase in total expenditure from $166 billion to $320 billion (an average annual growth of 3.33%). If people live longer without additional morbidity, then total health expenditure only grows at an average annual rate of 0.48%. If only some of those additional years are in good health, then the average year on year growth is 1.87%.

Conclusion

Ageing will have a direct effect on the growth of health spending but is likely to be dwarfed by other demand and supply factors. A focus on greater efficiency in health production and finance is likely to be more effective in delivering high quality care than trying to restrain the demand for health and aged care among the elderly.

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Translational Geroscience: From invertebrate models to companion animal and human interventions

Mitchell B. Lee, Matt Kaeberlein

Translational geroscience is an interdisciplinary field descended from basic gerontology that seeks to identify, validate, and clinically apply interventions to maximize healthy, disease-free lifespan. In this review, we describe a research pipeline for the identification and validation of lifespan extending interventions. Beginning in invertebrate model systems, interventions are discovered and then characterized using other invertebrate model systems (evolutionary translation), models of genetic diversity, and disease models. Vertebrate model systems, particularly mice, can then be utilized to validate interventions in mammalian systems. Collaborative, multi-site efforts, like the Interventions Testing Program (ITP), provide a key resource to assess intervention robustness in genetically diverse mice. Mouse disease models provide a tool to understand the broader utility of longevity interventions. Beyond mouse models, we advocate for studies in companion pets. The Dog Aging Project is an exciting example of translating research in dogs, both to develop a model system and to extend their healthy lifespan as a goal in itself. Finally, we discuss proposed and ongoing intervention studies in humans, unmet needs for validating interventions in humans, and speculate on how differences in survival among human populations may influence intervention efficacy.

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Dietary carbohydrate intake and mortality: a prospective cohort study and meta-analysis

Findings

During a median follow-up of 25 years there were 6283 deaths in the ARIC cohort, and there were 40 181 deaths across all cohort studies. In the ARIC cohort, after multivariable adjustment, there was a U-shaped association between the percentage of energy consumed from carbohydrate (mean 48·9%, SD 9·4) and mortality: a percentage of 50–55% energy from carbohydrate was associated with the lowest risk of mortality. In the meta-analysis of all cohorts (432 179 participants), both low carbohydrate consumption (<40%) and high carbohydrate consumption (>70%) conferred greater mortality risk than did moderate intake, which was consistent with a U-shaped association (pooled hazard ratio 1·20, 95% CI 1·09–1·32 for low carbohydrate consumption; 1·23, 1·11–1·36 for high carbohydrate consumption). However, results varied by the source of macronutrients: mortality increased when carbohydrates were exchanged for animal-derived fat or protein (1·18, 1·08–1·29) and mortality decreased when the substitutions were plant-based (0·82, 0·78–0·87).

Interpretation

Both high and low percentages of carbohydrate diets were associated with increased mortality, with minimal risk observed at 50–55% carbohydrate intake. Low carbohydrate dietary patterns favouring animal-derived protein and fat sources, from sources such as lamb, beef, pork, and chicken, were associated with higher mortality, whereas those that favoured plant-derived protein and fat intake, from sources such as vegetables, nuts, peanut butter, and whole-grain breads, were associated with lower mortality, suggesting that the source of food notably modifies the association between carbohydrate intake and mortality.

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Short-term feeding of a ketogenic diet induces more severe hepatic insulin resistance than a obesogenic high-fat diet

Gerald Grandl, Leon Straub, Carla Rudigier, Myrtha Arnold, Stephan Wueest, Daniel Konrad, Christian Wolfrum

Despite being a relevant healthcare issue and heavily investigated, the aetiology of type 2 diabetes (T2D) is still incompletely understood. It is well established that increased endogenous glucose production (EGP) leads to a progressive increase in glucose levels, causing insulin resistance and eventual loss of glucose homeostasis. The consumption of high carbohydrate, high-fat, western style diet (HFD) is linked to the development of T2D and obesity, whereas the consumption of a low carbohydrate, high-fat, ketogenic diet (KD) is considered healthy. However, several days of carbohydrate restriction are known to cause selective hepatic insulin resistance. In the present study, we compare the effects of short-term HFD and KD feeding on glucose homeostasis in mice. We show that, even though KD fed animals appear to be healthy in the fasted state, they exhibit decreased glucose tolerance to a greater extent than HFD fed animals. Furthermore, we show that this effect originates from blunted suppression of hepatic glucose production by insulin, rather than impaired glucose clearance and tissue glucose uptake. These data suggest that the early effects of HFD consumption on EGP may be part of a normal physiological response to increased lipid intake and oxidation, and that systemic insulin resistance results from the addition of dietary glucose to EGP-derived glucose.

Methionine Restriction Extends Lifespan in Progeroid Mice and Alters Lipid and Bile Acid Metabolism

Dietary intervention constitutes a feasible approach for modulating metabolism and improving the health span and lifespan. Methionine restriction (MR) delays the appearance of age-related diseases and increases longevity in normal mice. However, the effect of MR on premature aging remains to be elucidated. Here, we describe that MR extends lifespan in two different mouse models of Hutchinson-Gilford progeria syndrome (HGPS) by reversing the transcriptome alterations in inflammation and DNA-damage response genes present in this condition. Further, MR improves the lipid profile and changes bile acid levels and conjugation, both in wild-type and in progeroid mice. Notably, treatment with cholic acid improves the health span and lifespan *in vivo*. These results suggest the existence of a metabolic pathway involved in the longevity extension achieved by MR and support the possibility of dietary interventions for treating progeria.

A novel gene-diet pair modulates *C. elegans* aging

Sonia Verma, Urmila Jagtap, Anita Goyala, Arnab Mukhopadhyay

Diet profoundly affects metabolism and incidences of age-related diseases. Animals adapt their physiology to different food-types, modulating complex life-history traits like aging. The molecular mechanisms linking adaptive capacity to diet with aging are less known. We identify FLR-4 kinase as a novel modulator of aging in *C. elegans*, depending on bacterial diet. FLR-4 functions to prevent differential activation of the p38MAPK pathway in response to diverse food-types, thereby maintaining normal life span. In a kinase-dead *flr-4* mutant, *E. coli* HT115 (K12 strain), but not the standard diet OP50 (B strain), is able to activate p38MAPK, elevate expression of cytoprotective genes through the nuclear hormone receptor NHR-8 and enhance life span. Interestingly, *flr-4* and dietary restriction utilize similar pathways for longevity assurance, suggesting cross-talks between cellular modules that respond to diet quality and quantity. Together, our study discovers a new *C. elegans* gene-diet pair that controls the plasticity of aging.

Low intake of vitamin E accelerates cellular aging in patients with established cardiovascular disease: The CORDIOPREV study

Leukocyte telomere length (LTL) shortening is a biomarker of cellular aging that can be decelerated by diet. We aimed to investigate the effect of dietary intake of vitamin E on biomarkers of cellular senescence in patients with established cardiovascular disease. To this end, DNA from 1002 participants of the CORDIOPREV study (NCT00924937) was isolated and LTL wa s measured by real-time PCR. Dietary information was collected using a 146-item food frequency questionnaire, and several oxidative stress and damage biomarkers were determined. We found that patients with an inadequate intake of vitamin E according to the European Food Safety Authority, U.S. Food and Nutrition Board, and Spanish dietary recommendation had shorter LTL than those with an adequate intake (p=0.004, p=0.015 and p=0.005, respectively). Moreover, we observed a positive correlation between olive oil, fish consumption and LTL (r^2=0.083, p=0.010; r^2=0.090, p=0.006, respectively). Subjects who consumed more than 30 mL olive oil/day had longer LTL than subjects with lower consumption (p=0.013). Furthermore, we observed higher glutathione peroxidase activity in subjects consuming less vitamin E (p=0.031). Our findings support the importance of an adequate consumption of the antioxidant vitamin E, and the value of the diet as a modulating tool of the senescence process.

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A nutrient-induced affinity switch controls mTORC1 activation by its Rag GTPase–Ragulator lysosomal scaffold

A key step in nutrient sensing is activation of the master growth regulator, mTORC1 kinase, on the lysosomal membrane. Nutrients enable mTORC1 scaffolding by a complex composed of the Rag GTPases (Rags) and Ragulator, but the underlying mechanism of mTORC1 capture is poorly understood. Combining dynamic imaging in cells and reconstituted systems, we uncover an affinity switch that controls mTORC1 lifetime and activation at the lysosome. Nutrients destabilize the Rag–Ragulator interface, causing cycling of the Rags between lysosome-bound Ragulator and the cytoplasm, and rendering mTORC1 capture contingent on simultaneous engagement of two Rag-binding interfaces. Rag GTPase domains trigger cycling by coordinately weakening binding of the C-terminal domains to Ragulator in a nucleotide-controlled manner. Cancer-specific Rag mutants override release from Ragulator and enhance mTORC1 recruitment and signalling output. Cycling in the active state sets the Rags apart from most signalling GTPases, and provides a mechanism to attenuate mTORC1 signalling.

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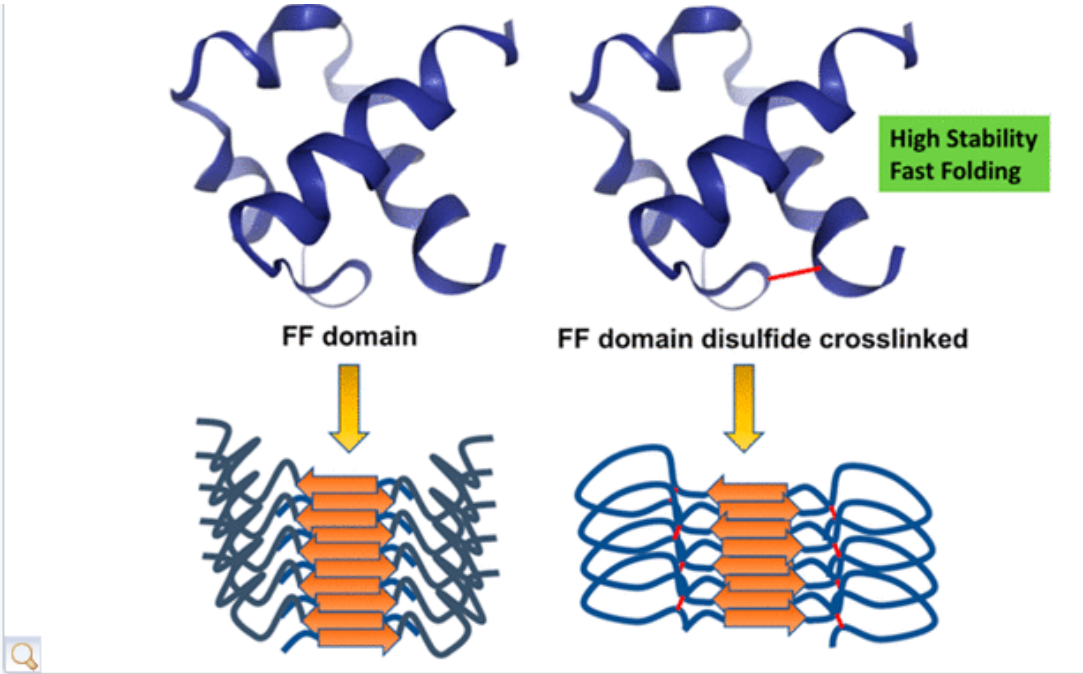
Rapamycin Confers Neuroprotection Against Aging-Induced Oxidative Stress, Mitochondrial Dysfunction, and Neurodegeneration in Old Rats Through Activation of Autophagy

Brain aging is an intricate and natural phenomenon exclusively characterized by oxidative stress, accumulation of oxidatively damaged macromolecules, and alterations in structure and function of neurons that further increase the risk factor for most of the neurodegenerative diseases. In addition, age-dependent defective autophagy has also been implicated to favor the pathogenesis and prevalence of the neurological diseases. Therefore, the development of strategies that delay aging and the concomitant neurological disorders remain elusive. Thus, the present study was undertaken to investigate the effect of rapamycin-induced activation of autophagy on aging-related oxidative stress, cell death, neuroinflammation, and neurodegeneration in rat brain. Our data demonstrated the significant age-related oxidative stress, apoptotic cell death, elevated inflammatory response, and reduced level of markers associated with rejuvenation and neural integrity, including the activities of ion channel transporters (Na^+/K^+-ATPase and Ca^{2+}-ATPase) and acetylcholinesterase in the brain of old aged rats. Furthermore, rapamycin (0.5 mg/kg b.w. for 28 days) induced activation of autophagy provided significant protection to aging rat brain by reducing the aging-induced oxidative stress, apoptotic cell death, and markers of neurodegeneration. Thus, our data confirmed that autophagy plays a pivotal role in delaying brain aging plausibly by maintaining the cellular homeostasis, and structural and functional integrity of cells in the brain.

Global Protein Stabilization Does Not Suffice to Prevent Amyloid Fibril Formation



Mutations or cellular conditions that destabilize the native protein conformation promote the population of partially unfolded conformations, which in many cases assemble into insoluble amyloid fibrils, a process associated with multiple human pathologies. Therefore, stabilization of protein structures is seen as an efficient way to prevent misfolding and subsequent aggregation. This has been suggested to be the underlying reason why proteins living in harsh environments, such as the extracellular space, have evolved disulfide bonds. The effect of protein disulfides on the thermodynamics and kinetics of folding has been extensively studied, but much less is known on its effect on aggregation reactions. Here, we designed a single point mutation that introduces a disulfide bond in the all-α FF domain, a protein that, despite being devoid of preformed β-sheets, forms β-sheet-rich amyloid fibrils. The novel and unique covalent bond in the FF domain dramatically increases its thermodynamic stability and folding speed. Nevertheless, these optimized properties cannot counteract the inherent aggregation propensity of the protein, thus indicating that a high global protein stabilization does not suffice to prevent amyloid formation unless it contributes to hide from exposure the specific regions that nucleate the aggregation reaction.

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Aging Cell. 2018 Aug 20:e12840. doi: 10.1111/acel.12840. [Epub ahead of print]

Tau protein aggregation is associated with cellular senescence in the brain.

Musi N[1,2,3], Valentine JM[1], Sickora KR[1], Baeuerle E[1], Thompson CS[1], Shen Q[4], Orr ME[1,2,3].

Author information

Abstract

Tau protein accumulation is the most common pathology among degenerative brain diseases, including Alzheimer's disease (AD), progressive supranuclear palsy (PSP), traumatic brain injury (TBI) and over twenty others. Tau-containing neurofibrillary tangle (NFT) accumulation is the closest correlate with cognitive decline and cell loss (Arriagada et al., 1992), yet mechanisms mediating tau toxicity are poorly understood. NFT formation does not induce apoptosis (de Calignon et al., 2009), which suggests secondary mechanisms are driving toxicity. Transcriptomic analyses of NFT-containing neurons microdissected from postmortem AD brain revealed an expression profile consistent with cellular senescence. This complex stress response induces aberrant cell cycle activity, adaptations to maintain survival, cellular remodeling, and metabolic dysfunction. Using four AD transgenic mouse models, we found that NFTs, but not Aβ plaques, display a senescence-like phenotype. Cdkn2a transcript level, a hallmark measure of senescence, directly correlated with brain atrophy and NFT burden in mice. This relationship extended to postmortem brain tissue from humans with PSP to indicate a phenomenon common to tau toxicity. Tau transgenic mice with late stage pathology were treated with senolytics to remove senescent cells. Despite the advanced age and disease progression, MRI brain imaging and histopathological analyses indicated a reduction in total NFT density, neuron loss and ventricular enlargement. Collectively, these findings indicate a strong association between the presence of NFTs and cellular senescence in the brain, which contributes to neurodegeneration. Given the prevalence of tau protein deposition among neurodegenerative diseases, these findings have broad implications for understanding, and potentially treating, dozens of brain diseases. This article is protected by copyright. All rights reserved.

Redox Biol. 2018 Sep;18:279-294. doi: 10.1016/j.redox.2018.07.010. Epub 2018 Jul 19.

Genetic ablation of tau improves mitochondrial function and cognitive abilities in the hippocampus.

Jara C[1], Aránguiz A[1], Cerpa W[2], Tapia-Rojas C[3], Quintanilla RA[4].

Author information

Abstract

Tau is a key protein for microtubule stability; however, post-translationally modified tau contributes to neurodegenerative diseases by forming tau aggregates in the neurons. Previous reports from our group and others have shown that pathological forms of tau are toxic and impair mitochondrial function, whereas tau deletion is neuroprotective. However, the effects of tau ablation on brain structure and function in young mice have not been fully elucidated. Therefore, the aim of this study was to investigate the implications of tau ablation on the mitochondrial function and cognitive abilities of a litter of young mice (3 months old). Our results showed that tau deletion had positive effects on hippocampal cells by decreasing oxidative damage, favoring a mitochondrial pro-fusion state, and inhibiting mitochondrial permeability transition pore (mPTP) formation by reducing cyclophilin D (Cyp-D) protein. More importantly, tau deletion increased ATP production and improved the recognition memory and attentive capacity of juvenile mice. Therefore, the absence of tau enhanced brain function by improving mitochondrial health, which supplied more energy to the synapses. Thus, our work opens the possibility that preventing negative tau modifications could enhance brain function through the improvement of mitochondrial health.

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A Single-Cell Transcriptome Atlas of the Aging Drosophila Brain

The diversity of cell types and regulatory states in the brain, and how these change during aging, remains largely unknown. We present a single-cell transcriptome atlas of the entire adult *Drosophila melanogaster* brain sampled across its lifespan. Cell clustering identified 87 initial cell clusters that are further subclustered and validated by targeted cell-sorting. Our data show high granularity and identify a wide range of cell types. Gene network analyses using SCENIC revealed regulatory heterogeneity linked to energy consumption. During aging, RNA content declines exponentially without affecting neuronal identity in old brains. This single-cell brain atlas covers nearly all cells in the normal brain and provides the tools to study cellular diversity alongside other *Drosophila* and mammalian single-cell datasets in our unique single-cell analysis platform: *SCope* (http://scope.aertslab.org). These results, together with *SCope*, allow comprehensive exploration of all transcriptional states of an entire aging brain.

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AAV9-mediated telomerase activation does not accelerate tumorigenesis in the context of oncogenic K-Ras-induced lung cancer

Miguel A. Muñoz-Lorente, Paula Martínez, Águeda Tejera, Kurt Whittemore, Ana Carolina Moisés-Silva, Fàtima Bosch,

Short and dysfunctional telomeres are sufficient to induce a persistent DNA damage response at chromosome ends, which leads to the induction of senescence and/or apoptosis and to various age-related conditions, including a group of diseases known as "telomere syndromes", which are provoked by extremely short telomeres owing to germline mutations in telomere genes. This opens the possibility of using telomerase activation as a potential therapeutic strategy to rescue short telomeres both in telomere syndromes and in age-related diseases, in this manner maintaining tissue homeostasis and ameliorating these diseases. In the past, we generated adeno-associated viral vectors carrying the telomerase gene (AAV9-*Tert*) and shown their therapeutic efficacy in mouse models of cardiac infarct, aplastic anemia, and pulmonary fibrosis. Although we did not observe increased cancer incidence as a consequence of Tert overexpression in any of those models, here we set to test the safety of AAV9-mediated Tert overexpression in the context of a cancer prone mouse model, owing to expression of oncogenic K-ras. As control, we also treated mice with AAV9 vectors carrying a catalytically inactive form of Tert, known to inhibit endogenous telomerase activity. We found that overexpression of Tert does not accelerate the onset or progression of lung carcinomas, even when in the setting of a p53-null background. These findings indicate that telomerase activation by using AAV9-mediated *Tert* gene therapy has no detectable cancer-prone effects in the context of oncogene-induced mouse tumors.

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A Zombie *LIF* Gene in Elephants Is Upregulated by TP53 to Induce Apoptosis in Response to DNA Damage

Large-bodied organisms have more cells that can potentially turn cancerous than small-bodied organisms, imposing an increased risk of developing cancer. This expectation predicts a positive correlation between body size and cancer risk; however, there is no correlation between body size and cancer risk across species ("Peto's paradox"). Here, we show that elephants and their extinct relatives (proboscideans) may have resolved Peto's paradox in part through refunctionalizing a leukemia inhibitory factor pseudogene (*LIF6*) with pro-apoptotic functions. *LIF6* is transcriptionally upregulated by TP53 in response to DNA damage and translocates to the mitochondria where it induces apoptosis. Phylogenetic analyses of living and extinct proboscidean *LIF6* genes indicates that its TP53 response element evolved coincident with the evolution of large body sizes in the proboscidean stem lineage. These results suggest that refunctionalizing of a pro-apoptotic LIF pseudogene may have been permissive (although not sufficient) for the evolution of large body sizes in proboscideans.

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TBK1 Suppresses RIPK1-Driven Apoptosis and Inflammation during Development and in Aging

Aging is a major risk factor for both genetic and sporadic neurodegenerative disorders. However, it is unclear how aging interacts with genetic predispositions to promote neurodegeneration. Here, we investigate how partial loss of function of TBK1, a major genetic cause for amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) comorbidity, leads to age-dependent neurodegeneration. We show that TBK1 is an endogenous inhibitor of RIPK1 and the embryonic lethality of *Tbk1* $^{-/-}$ mice is dependent on RIPK1 kinase activity. In aging human brains, another endogenous RIPK1 inhibitor, TAK1, exhibits a marked decrease in expression. We show that in *Tbk1* $^{+/-}$ mice, the reduced myeloid TAK1 expression promotes all the key hallmarks of ALS/FTD, including neuroinflammation, TDP-43 aggregation, axonal degeneration, neuronal loss, and behavior deficits, which are blocked upon inhibition of RIPK1. Thus, aging facilitates RIPK1 activation by reducing TAK1 expression, which cooperates with genetic risk factors to promote the onset of ALS/FTD.

Methylglyoxal-derived posttranslational arginine modifications are abundant histone marks

Histone posttranslational modifications (PTMs) regulate chromatin dynamics, DNA accessibility, and transcription to expand the genetic code. Many of these PTMs are produced through cellular metabolism to offer both feedback and feedforward regulation. Herein we describe the existence of Lys and Arg modifications on histones by a glycolytic by-product, methylglyoxal (MGO). Our data demonstrate that adduction of histones by MGO is an abundant modification, present at the same order of magnitude as Arg methylation. These modifications were detected on all four core histones at critical residues involved in both nucleosome stability and reader domain binding. In addition, MGO treatment of cells lacking the major detoxifying enzyme, glyoxalase 1, results in marked disruption of H2B acetylation and ubiquitylation without affecting H2A, H3, and H4 modifications. Using RNA sequencing, we show that MGO is capable of altering gene transcription, most notably in cells lacking GLO1. Finally, we show that the deglycase DJ-1 protects histones from adduction by MGO. Collectively, our findings demonstrate the existence of a previously undetected histone modification derived from glycolysis, which may have far-reaching implications for the control of gene expression and protein transcription linked to metabolism.

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A study paradigm integrating prospective epidemiologic cohorts and electronic health records to identify disease biomarkers

Defining the full spectrum of human disease associated with a biomarker is necessary to advance the biomarker into clinical practice. We hypothesize that associating biomarker measurements with electronic health record (EHR) populations based on shared genetic architectures would establish the clinical epidemiology of the biomarker. We use Bayesian sparse linear mixed modeling to calculate SNP weightings for 53 biomarkers from the Atherosclerosis Risk in Communities study. We use the SNP weightings to computed predicted biomarker values in an EHR population and test associations with 1139 diagnoses. Here we report 116 associations meeting a Bonferroni level of significance. A false discovery rate (FDR)-based significance threshold reveals more known and undescribed associations across a broad range of biomarkers, including biometric measures, plasma proteins and metabolites, functional assays, and behaviors. We confirm an inverse association between LDL-cholesterol level and septicemia risk in an independent epidemiological cohort. This approach efficiently discovers biomarker-disease associations.

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Reduced insulin/IGF-1 signalling in adult parents increases offspring fitness

Martin I Lind, Sanjana Ravindran, Zuzana Sekajova, Hanne Carlsson, Andrea Hinas, Alexei A Maklakov

doi: https://doi.org/10.1101/405019

Reduced expression of the insulin/insulin-like nutrient-sensing signalling (IIS) pathway gene daf-2 in adult Caenorhabditis elegans nematode worms increases longevity without affecting fecundity, but the effect of parental lifespan extension on adult offspring is largely unknown. Here we show that reduced IIS signalling in parental generation increases offspring fitness. We used RNA interference (RNAi) to silence daf-2 expression in sexually mature C. elegans hermaphrodites from three different genotypes: N2 wildtype, as well as ppw-1 and rrf-1 mutants that are deficient for RNAi in germline and soma, respectively. Long-lived daf-2 RNAi parents showed normal fecundity as self-fertilizing hermaphrodites and improved late-life reproduction when mated to males. Remarkably, the offspring of daf-2 RNAi parents produced more progeny and had higher Darwinian fitness across all three genotypes. Thus, reduced IIS signalling in adulthood improves offspring quality supporting the emerging view that suboptimally high levels of nutrient-sensing signalling in late-life lie at the heart of ageing.

Reactive oxygen species extend insect life span using components of the insulin-signaling pathway

Reactive oxygen species (ROS) are well-known accelerants of aging, but, paradoxically, we show that physiological levels of ROS extend life span in pupae of the moth *Helicoverpa armigera*, resulting in the dormant state of diapause. This developmental switch appears to operate through a variant of the conventional insulin-signaling pathway, as evidenced by the facts that Akt, p-Akt, and PRMT1 are elevated by ROS, but not insulin, and that high levels of p-Akt fail to phosphorylate FoxO through PRMT1-mediated methylation. These results suggest a distinct signaling pathway culminating in the elevation of FoxO, which in turn promotes the extension of life span characteristic of diapause.

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C. elegans Eats Its Own Intestine to Make Yolk Leading to Multiple Senescent Pathologies

Aging (senescence) is characterized by the development of numerous pathologies, some of which limit lifespan. Key to understanding aging is discovery of the mechanisms (etiologies) that cause senescent pathology. In *C. elegans*, a major senescent pathology of unknown etiology is atrophy of its principal metabolic organ, the intestine. Here we identify a cause of not only this pathology but also of yolky lipid accumulation and redistribution (a form of senescent obesity): autophagy-mediated conversion of intestinal biomass into yolk. Inhibiting intestinal autophagy or vitellogenesis rescues both visceral pathologies and can also extend lifespan. This defines a disease syndrome leading to multimorbidity and contributing to late-life mortality. Activation of gut-to-yolk biomass conversion by insulin/IGF-1 signaling (IIS) promotes reproduction and senescence. This illustrates how major, IIS-promoted senescent pathologies in *C. elegans* can originate not from damage accumulation but from direct effects of futile, continued action of a wild-type biological program (vitellogenesis).

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Naked mole-rat transcriptome signatures of socially suppressed sexual maturation and links of reproduction to aging

Results

Comparative transcriptome analysis of tissue samples from ten organs showed, in contrast to GPs, low levels of differentiation between sexes in adult NMR non-breeders. After transition into breeders, NMR transcriptomes are markedly sex-specific, show pronounced feedback signaling via gonadal steroids, and have similarities to reproductive phenotypes in African cichlid fish, which also exhibit social status changes between dominant and subordinate phenotypes. Further, NMRs show functional enrichment of status-related expression differences associated with aging. Lipid metabolism and oxidative phosphorylation—molecular networks known to be linked to aging—were identified among most affected gene sets. Remarkably and in contrast to GPs, transcriptome patterns associated with longevity are reinforced in NMR breeders.

Conclusion

Our results provide comprehensive and unbiased molecular insights into interspecies differences between NMRs and GPs, both in sexual maturation and in the impact of reproduction on longevity. We present molecular evidence that sexual maturation in NMRs is socially suppressed. In agreement with evolutionary theories of aging in eusocial organisms, we have identified transcriptome patterns in NMR breeders that—in contrast to the disposable soma theory of aging—may slow down aging rates and potentially contribute to their exceptional long life- and healthspan.

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Species comparison of liver proteomes reveals links to naked mole-rat longevity and human aging

Mammals display a wide range of variation in their lifespan. Investigating the molecular networks that distinguish long- from short-lived species has proven useful to identify determinants of longevity. Here, we compared the livers of young and old long-lived naked mole-rats (NMRs) and the phylogenetically closely related, shorter-lived, guinea pigs using an integrated omics approach.

Results

We found that NMR livers display a unique expression pattern of mitochondrial proteins that results in distinct metabolic features of their mitochondria. For instance, we observed a generally reduced respiration rate associated with lower protein levels of respiratory chain components, particularly complex I, and increased capacity to utilize fatty acids. Interestingly, we show that the same molecular networks are affected during aging in both NMRs and humans, supporting a direct link to the extraordinary longevity of both species. Finally, we identified a novel detoxification pathway linked to longevity and validated it experimentally in the nematode *Caenorhabditis elegans*.

Conclusions

Our work demonstrates the benefits of integrating proteomic and transcriptomic data to perform cross-species comparisons of longevity-associated networks. Using a multispecies approach, we show at the molecular level that livers of NMRs display progressive age-dependent changes that recapitulate typical signatures of aging despite the negligible senescence and extraordinary longevity of these rodents.

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High protein intake is associated with low plasma NAD^+ levels in a healthy human cohort

Neda Seyedsadjadi, Jade Berg, Ayse A. Bilgin, Nady Braidy, Chris Salonikas, Ross Grant

High protein intake and reduced levels of the essential pyridine nucleotide nicotinamide adenine dinucleotide (NAD^+) have both been independently associated with promotion of the ageing phenotype. However, it has not yet been shown whether these two independent observations are biochemically linked. To investigate this possibility, we used a cross-sectional study design of 100 apparently healthy middle-aged males (n = 48) and females, in which we assessed average dietary intakes of multiple components using a validated questionnaire. We also analysed fasting blood levels of urea, NAD^+ and its metabolites, and inflammation-linked biomarkers, including interleukin-6 (IL-6), Kynurenine (Kyn), and Tryptophan (Trp). One-way ANOVA and ANCOVA were then performed for statistical analysis. Our results have shown for the first time that plasma levels of NAD^+ and Total NAD(H) were lower with increasing protein intake ($F(2, 92) = 4.61$, $P = 0.012$; $F(2, 92) = 4.55$, $P = 0.013$, respectively). The associated decrease in NAD^+ and NAD(H) levels was even stronger with increasing plasma levels of the protein breakdown product urea ($F(2, 93) = 25.11$, $P \leq 0.001$; $F(2, 93) = 21.10$, $P \leq 0.001$). These associations were all independent of age, gender and energy intake. However, no significant association was observed between protein intake or plasma urea, and plasma levels of NAD^+ metabolites. We also observed that plasma levels of the inflammatory cytokine IL-6, and both Kyn, and Trp, but not the Kyn/Trp ratio were higher with increasing plasma urea levels ($F(2, 94) = 3.30$, $P = 0.041$; $F(2, 95) = 7.41$, $P \leq 0.001$; $F(2, 96) = 4.23$, $P = 0.017$, respectively). These associations were dependent on eGFR and energy intake, except for the urea and Trp association that was independent of all. In conclusion, we report for the first time, a novel association between protein intake, its metabolism, and plasma NAD^+ levels with a possible link to inflammation. These findings provide further insight into how protein restriction may contribute to the anti-ageing process observed in several studies.

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Rejuvenation Res. 2018 Aug 19. doi: 10.1089/rej.2018.2077. [Epub ahead of print]

The Plasma NAD+ Metabolome is Dysregulated in 'normal' Ageing.

Clement J[1], Wong M[2], Poljak A[3], Sachdev P[4], Braidy N[5].

⊕ Author information

Abstract

Nicotinamide adenine dinucleotide (NAD+) is an essential pyridine nucleotide that serves as an electron carrier in cellular metabolism and plays a crucial role in the maintenance of balanced redox homeostasis. Quantification of NAD+:NADH and NADP+:NADPH ratios are pivotal to a wide variety of cellular processes, including intracellular secondary messenger signalling by CD38 glycohydrolases, DNA repair by poly(adenosine diphosphate ribose) polymerase (PARP), epigenetic regulation of gene expression by NAD-dependent histone deacetylase enzymes known as sirtuins, and regulation of the oxidative pentose phosphate pathway. We quantified changes in the NAD+ metabolome in plasma samples collected from consenting healthy human subjects across a wide age range (20-85 years) using liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS). Our data shows a significant decline in the plasma levels of NAD+, NADP+, and other important metabolites including nicotinamide mononucleotide (NMN) and nicotinic acid adenine dinucleotide (NAAD) with age. However, an age-related increase in the reduced form of NAD+ and NADP+ - NADH and NADPH - and nicotinamide (NAM), N-methyl-nicotinamide (MeNAM), and the products of adenosine diphosphoribosylation, including ADP-ribose (ADPR) was also reported. No significant differences were reported across age for nicotinic acid (NA) and nicotinic acid mononucleotide (NAMN). Taken together, our data cumulatively suggests that age-related impairments may also be associated with alterations in the extracellular plasma NAD+ metabolome.

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Am J Clin Nutr. 2018 Aug 1;108(2):343-353. doi: 10.1093/ajcn/nqy132.

A randomized placebo-controlled clinical trial of nicotinamide riboside in obese men: safety, insulin-sensitivity, and lipid-mobilizing effects.

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Author information

Abstract

BACKGROUND: Animal studies suggest a positive role for nicotinamide riboside (NR) on insulin sensitivity and hepatic steatosis in models of obesity and type 2 diabetes. NR, an NAD+ precursor, is a member of the vitamin B-3 family now available as an over-the-counter supplement. Although data from preclinical trials appear consistent, potential effects and safety need to be evaluated in human clinical trials.

OBJECTIVE: The aim of this study was to test the safety of dietary NR supplementation over a 12-wk period and potential to improve insulin sensitivity and other metabolic parameters in obese, insulin-resistant men.

DESIGN: In an investigator-initiated randomized, placebo-controlled, double-blinded, and parallel-group designed clinical trial, forty healthy, sedentary men with a body mass index (BMI) > 30 kg/m2, age-range 40-70 y were randomly assigned to 12 wk of NR (1000 mg twice daily) or placebo. We determined the effects of NR supplementation on insulin sensitivity by a hyperinsulinemic euglycemic clamp and substrate metabolism by indirect calorimetry and labeled substrates of tritiated glucose and palmitate. Body composition and fat mass distribution were determined by whole-body dual-energy X-ray absorptiometry (DXA) and MRI scans, and measurements of intrahepatic lipid content were obtained by MR spectroscopy.

RESULTS: Insulin sensitivity, endogenous glucose production, and glucose disposal and oxidation were not improved by NR supplementation. Similarly, NR supplementation had no effect on resting energy expenditure, lipolysis, oxidation of lipids, or body composition. No serious adverse events due to NR supplementation were observed and safety blood tests were normal.

CONCLUSION: 12 wk of NR supplementation in doses of 2000 mg/d appears safe, but does not improve insulin sensitivity and whole-body glucose metabolism in obese, insulin-resistant men. This trial was registered at clinicaltrials.gov as NCT02303483.

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Nicotinamide riboside supplementation dysregulates redox and energy metabolism in rats: Implications for exercise performance

Nicotinamide riboside is a recently discovered form of vitamin B_3 that can increase NAD(P) levels. NAD(P) plays key roles in energy metabolism, and its main function is the transfer of electrons in various cellular reactions. Research in aged or diseased mice reported that nicotinamide riboside increases NAD(H) levels, reduces morbidity and improves health and muscle function. We have recently shown that in healthy young rats, chronic administration of nicotinamide riboside marginally non-significantly decreased exercise performance by 35% ($P = 0.071$). As a follow-up to this finding, we analysed samples from these animals, in an attempt to reveal the potential mechanisms driving this adverse effect, focusing on redox homeostasis and bioenergetics. Thirty-eight Wistar rats were divided into four groups: control ($n = 10$), exercise ($n = 9$), nicotinamide riboside ($n = 10$) and exercise plus nicotinamide riboside ($n = 9$). Nicotinamide riboside was administered for 21 days [300 mg (kg body weight)$^{-1}$ daily]. At the end of administration, the exercise and the exercise plus nicotinamide riboside groups performed an incremental swimming performance test until exhaustion. Nicotinamide riboside supplementation increased the levels of NADPH in the liver ($P = 0.050$), increased the levels of F_2-isoprostanes in plasma ($P = 0.047$), decreased the activity of glutathione peroxidase ($P = 0.017$), glutathione reductase ($P < 0.001$) and catalase ($P = 0.024$) in erythrocytes, increased the level of glycogen in the liver ($P < 0.001$) and decreased the concentration of glucose ($P = 0.016$) and maximal lactate accumulation in plasma ($P = 0.084$). These findings support the prevailing idea that exogenously administered redox agents in heathy populations might lead to adverse effects and not necessarily to beneficial or neutral effects.

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Bioessays. 2018 Aug;40(8):e1800005. doi: 10.1002/bies.201800005. Epub 2018 Jun 14.

The Energy Maintenance Theory of Aging: Maintaining Energy Metabolism to Allow Longevity.

Chaudhari SN[1], Kipreos ET[1].

Author information

Abstract

Fused, elongated mitochondria are more efficient in generating ATP than fragmented mitochondria. In diverse C. elegans longevity pathways, increased levels of fused mitochondria are associated with lifespan extension. Blocking mitochondrial fusion in these animals abolishes their extended longevity. The long-lived C. elegans vhl-1 mutant is an exception that does not have increased fused mitochondria, and is not dependent on fusion for longevity. Loss of mammalian VHL upregulates alternate energy generating pathways. This suggests that mitochondrial fusion facilitates longevity in C. elegans by increasing energy metabolism. In diverse animals, ATP levels broadly decreases with age. Substantial evidence supports the theory that increasing or maintaining energy metabolism promotes the survival of older animals. Increased ATP levels in older animals allow energy-intensive repair and homeostatic mechanisms such as proteostasis that act to prevent cellular aging. These observations support the emerging paradigm that maintaining energy metabolism promotes the survival of older animals.

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J Gerontol A Biol Sci Med Sci. 2018 Aug 27. doi: 10.1093/gerona/gly193. [Epub ahead of print]

Redox modulating factors impact longevity regulation in rotifers.

Macsai L[1], Olah Z[1], Bush AI[2], Galik B[3], Onody R[4], Kalman J[1], Datki Z[1].

⊕ Author information

Abstract

Rotifers are microinvertebrate models to study the phylogenetically based mechanisms of aging. Our study aimed to develop a physiological system with electron deprivation via a chemical electron carrier/acceptor pair together with extreme caloric restriction (ECR). Middle-aged Philodina acuticornis rotifers were treated with combinations of phenazine methosulfate (PMS, electron carrier) and 2,3-bis(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide inner salt (XTT, electron acceptor) for a period of 72 h under total food deprivation (preselection). The ability of XTT to be reduced was confirmed both in vitro (with NADH) and in vivo (with live rotifers). Subsequently, the respective electron acceptor alone at a lower dose was administered in combination with ECR for several months on preselected survivors. We found that the longevity of rotifers markedly increased (4x) after PMS/XTT/total food deprivation preselection followed by XTT/ECR treatment. Ascorbic acid in equivalent concentrations caused similar but less pronounced tendencies. The synergistic effect of chemical electron deprivation and ECR caused delayed aging and the development of an outstanding phenotype that we refer to as 'super rotifers', characterized by increased longevity and retained reproductive ability compared to normal middle-aged individuals. The presented model provides new insights into the connection between redox modulation and age-related features in vivo.

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Geroscience. 2018 Aug 18. doi: 10.1007/s11357-018-0039-6. [Epub ahead of print]

Thioredoxin overexpression in both the cytosol and mitochondria accelerates age-related disease and shortens lifespan in male C57BL/6 mice.

Cunningham GM[1], Flores LC[1], Roman MG[1], Cheng C[1], Dube S[1], Allen C[1], Valentine JM[1], Hubbard GB[1,2], Bai Y[3], Saunders TL[4], Ikeno Y[5,6,7,8].

⊕ Author information

Abstract

To investigate the role of increased levels of thioredoxin (Trx) in both the cytosol (Trx1) and mitochondria (Trx2) on aging, we have conducted a study to examine survival and age-related diseases using male mice overexpressing Trx1 and Trx2 (TXNTg × TXN2Tg). Our study demonstrated that the upregulation of Trx in both the cytosol and mitochondria in male TXNTg × TXN2Tg C57BL/6 mice resulted in a significantly shorter lifespan compared to wild-type (WT) mice. Cross-sectional pathology data showed a slightly higher incidence of neoplastic diseases in TXNTg × TXN2Tg mice than WT mice. The incidence of lymphoma, a major neoplastic disease in C57BL/6 mice, was slightly higher in TXNTg × TXN2Tg mice than in WT mice, and more importantly, the severity of lymphoma was significantly higher in TXNTg × TXN2Tg mice compared to WT mice. Furthermore, the total number of histopathological changes in the whole body (disease burden) was significantly higher in TXNTg × TXN2Tg mice compared to WT mice. Therefore, our study suggests that overexpression of Trx in both the cytosol and mitochondria resulted in deleterious effects on aging and accelerated the development of age-related diseases, especially cancer, in male C57BL/6 mice.

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Proximal Cysteines that Enhance Lysine *N*-Acetylation of Cytosolic Proteins in Mice Are Less Conserved in Longer-Living Species

Acetyl-coenzyme A (CoA) is an abundant metabolite that can also alter protein function through non-enzymatic *N*-acetylation of protein lysines. This *N*-acetylation is greatly enhanced *in vitro* if an adjacent cysteine undergoes initial *S*-acetylation, as this can lead to *S*→*N* transfer of the acetyl moiety. Here, using modeled mouse structures of 619 proteins *N*-acetylated in mouse liver, we show lysine *N*-acetylation is greater *in vivo* if a cysteine is within ~10 Å. Extension to the genomes of 52 other mammalian and bird species shows pairs of proximal cysteine and *N*-acetylated lysines are less conserved, implying most *N*-acetylation is detrimental. Supporting this, there is less conservation of cytosolic pairs of proximal cysteine and *N*-acetylated lysines in species with longer lifespans. As acetyl-CoA levels are linked to nutrient supply, these findings suggest how dietary restriction could extend lifespan and how pathologies resulting from dietary excess may occur.

REVIEWS/COMMENTS/ METHODS/EDITORIALS

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nature REVIEWS DRUG DISCOVERY

News and Analysis | Published: 03 August 2018

Anti-ageing pipeline starts to mature

Asher Mullard

Nature Reviews Drug Discovery **17**, 609–612 (2018) | Download Citation

Ongoing and upcoming clinical trials of metformin, mTOR inhibitors and senescent cell-killing drugs could prove that ageing and ageing-related diseases are viable drug discovery indications.

The promise of a Fountain of Youth has captivated and eluded explorers for millennia. Researchers now hope that clinical trials could point the way to drugs that can achieve the same effect, blunting the ravages of ageing — or at least delaying the onset and progression of ageing-related diseases (Table 1).

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Does Calorie Restriction in Primates Increase Lifespan? Revisiting Studies on Macaques (*Macaca mulatta*) and Mouse Lemurs (*Microcebus murinus*)

Eric Le Bourg

The effects of calorie restriction have now been studied in two non-human primates, the macaque *Macaca mulatta* and the mouse lemur *Microcebus murinus*. The study on lemurs and one of the two studies on macaques have reported a lifespan increase. In this review, I argue that these results are better explained by a lifespan decrease in the control group because of a bad diet and/or overfeeding, rather than by a real lifespan increase in calorie-restricted animals. If these results can be readily translated to humans, it would mean that no beneficial effect of calorie restriction on lifespan can be expected in normal-weight or lean people, but that overweight and/or obese people could benefit to some extent from a decrease in excessive food intake.

Promoting the clearance of neurotoxic proteins in neurodegenerative disorders of ageing

Neurodegenerative disorders of ageing (NDAs) such as Alzheimer disease, Parkinson disease, frontotemporal dementia, Huntington disease and amyotrophic lateral sclerosis represent a major socio-economic challenge in view of their high prevalence yet poor treatment. They are often called 'proteinopathies' owing to the presence of misfolded and aggregated proteins that lose their physiological roles and acquire neurotoxic properties. One reason underlying the accumulation and spread of oligomeric forms of neurotoxic proteins is insufficient clearance by the autophagic–lysosomal network. Several other clearance pathways are also compromised in NDAs: chaperone-mediated autophagy, the ubiquitin–proteasome system, extracellular clearance by proteases and extrusion into the circulation via the blood–brain barrier and glymphatic system. This article focuses on emerging mechanisms for promoting the clearance of neurotoxic proteins, a strategy that may curtail the onset and slow the progression of NDAs.

Mitochondrial Complex I Activity Is Required for Maximal Autophagy

Cells adapt to nutrient and energy deprivation by inducing autophagy, which is regulated by the mammalian target of rapamycin (mTOR) and AMP-activated protein kinases (AMPKs). We found that cell metabolism significantly influences the ability to induce autophagy, with mitochondrial complex I function being an important factor in the initiation, amplitude, and duration of the response. We show that phenformin or genetic defects in complex I suppressed autophagy induced by mTOR inhibitors, whereas autophagy was enhanced by strategies that increased mitochondrial metabolism. We report that mTOR inhibitors significantly increased select phospholipids and mitochondrial-associated membranes (MAMs) in a complex I-dependent manner. We attribute the complex I autophagy defect to the inability to increase MAMs, limiting phosphatidylserine decarboxylase (PISD) activity and mitochondrial phosphatidylethanolamine (mtPE), which support autophagy. Our data reveal the dynamic and metabolic regulation of autophagy.

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The physiology of endocrine systems with ageing

During ageing, the secretory patterns of the hormones produced by the hypothalamic–pituitary axis change, as does the sensitivity of the axis to negative feedback by end hormones. Additionally, glucose homoeostasis tends towards disequilibrium with increasing age. Along with these endocrine alterations, a loss of bone and muscle mass and strength occurs, coupled with an increase in fat mass. In addition, ageing-induced effects are difficult to disentangle from the influence of other factors that are common in older people, such as chronic diseases, inflammation, and low nutritional status, all of which can also affect endocrine systems. Traditionally, the decrease in hormone activity during the ageing process has been considered to be detrimental because of the related decline in bodily functions. The concept of hormone replacement therapy was suggested as a therapeutic intervention to stop or reverse this decline. However, clearly some of these changes are a beneficial adaptation to ageing, whereas hormonal intervention often causes important adverse effects. In this paper, we discuss the effects of age on the different hypothalamic–pituitary–hormonal organ axes, as well as age-related changes in calcium and bone metabolism and glucose homoeostasis.

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Mechanisms of Insulin Action and Insulin Resistance

Max C. Petersen and Gerald I. Shulman

The 1921 discovery of insulin was a Big Bang from which a vast and expanding universe of research into insulin action and resistance has issued. In the intervening century, some discoveries have matured, coalescing into solid and fertile ground for clinical application; others remain incompletely investigated and scientifically controversial. Here, we attempt to synthesize this work to guide further mechanistic investigation and to inform the development of novel therapies for type 2 diabetes (T2D). The rational development of such therapies necessitates detailed knowledge of one of the key pathophysiological processes involved in T2D: insulin resistance. Understanding insulin resistance, in turn, requires knowledge of normal insulin action. In this review, both the physiology of insulin action and the pathophysiology of insulin resistance are described, focusing on three key insulin target tissues: skeletal muscle, liver, and white adipose tissue. We aim to develop an integrated physiological perspective, placing the intricate signaling effectors that carry out the cell-autonomous response to insulin in the context of the tissue-specific functions that generate the coordinated organismal response. First, in section II, the effectors and effects of direct, cell-autonomous insulin action in muscle, liver, and white adipose tissue are reviewed, beginning at the insulin receptor and working downstream. Section III considers the critical and underappreciated role of tissue crosstalk in whole body insulin action, especially the essential interaction between adipose lipolysis and hepatic gluconeogenesis. The pathophysiology of insulin resistance is then described in section IV. Special attention is given to which signaling pathways and functions become insulin resistant in the setting of chronic overnutrition, and an alternative explanation for the phenomenon of "selective hepatic insulin resistance" is presented. Sections V, VI, and VII critically examine the evidence for and against several putative mediators of insulin resistance. Section V reviews work linking the bioactive lipids diacylglycerol, ceramide, and acylcarnitine to insulin resistance; section VI considers the impact of nutrient stresses in the endoplasmic reticulum and mitochondria on insulin resistance; and section VII discusses non-cell autonomous factors proposed to induce insulin resistance, including inflammatory mediators, branched-chain amino acids, adipokines, and hepatokines. Finally, in section VIII, we propose an integrated model of insulin resistance that links these mediators to final common pathways of metabolite-driven gluconeogenesis and ectopic lipid accumulation.

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"The Same Thing That Makes You Live Can Kill You in the End": Exploring the Effects of Growth Rates and Longevity on Cellular Metabolic Rates and Oxidative Stress in Mammals and Birds

All aerobic organisms are subjected to metabolic by-products known as reactive species (RS). RS can wreak havoc on macromolecules by structurally altering proteins and inducing mutations in DNA, among other deleterious effects. To combat accumulating damage, organisms have an antioxidant system to sequester RS before they cause cellular damage. The balance between RS production, antioxidant defences, and accumulated cellular damage is termed oxidative stress. Physiological ecologists, gerontologists, and metabolic biochemists have turned their attention to whether oxidative stress is the principal, generalized mechanism that mediates and limits longevity, growth rates, and other life-history trade-offs in animals, as may be the case in mammals and birds. At the crux of this theory lies the regulation and activities of the mitochondria with respect to the organism and its metabolic rate. At the whole-animal level, evolutionary theory suggests that developmental trajectories and growth rates can shape the onset and rate of aging. Mitochondrial function is important for aging since it is the main source of energy in cells, and the main source of RS. Altering oxidative stress levels, either increase in oxidative damage or reduction in antioxidants, has proven to also decrease growth rates, which implies that oxidative stress is a cost of, as well as a constraint on, growth. Yet, in nature, many animals exhibit fast growth rates that lead to higher loads of oxidative stress, which are often linked to shorter lifespans. In this article, I summarize the latest findings on whole-animal life history trade-offs, such as growth rates and longevity, and how these can be affected by mitochondrial cellular metabolism, and oxidative stress.

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Curr Opin Cell Biol. 2018 Jun 13;54:121-129. doi: 10.1016/j.ceb.2018.05.016. [Epub ahead of print]

Tissue aging: the integration of collective and variant responses of cells to entropic forces over time.

Todhunter ME[1], Sayaman RW[1], Miyano M[1], LaBarge MA[2].

⊕ Author information

Abstract

Aging is driven by unavoidable entropic forces, physicochemical in nature, that damage the raw materials that constitute biological systems. Single cells experience and respond to stochastic physicochemical insults that occur either to the cells themselves or to their microenvironment, in a dynamic and reciprocal manner, leading to increased age-related cell-to-cell variation. We will discuss the biological mechanisms that integrate cell-to-cell variation across tissues resulting in stereotypical phenotypes of age.

Nucleolar Function in Lifespan Regulation

Varnesh Tiku [1, 3], Adam Antebi [1, 2]

The nucleolus is a prominent membraneless organelle residing within the nucleus. The nucleolus has been regarded as a housekeeping structure mainly known for its role in ribosomal RNA (rRNA) production and ribosome assembly. However, accumulating evidence has revealed its functions in numerous cellular processes that control organismal physiology, thereby taking the nucleolus much beyond its conventional role in ribosome biogenesis. Perturbations in nucleolar functions have been associated with severe diseases such as cancer and progeria. Recent studies have also uncovered the role of the nucleolus in development and aging. In this review we discuss major nucleolar functions that impact organismal aging.

J Cell Physiol. 2018 Aug 5. doi: 10.1002/jcp.26956. [Epub ahead of print]

Cellular senescence: Molecular mechanisms and pathogenicity.

Wei W[1,2], Ji S[1].

Author information

Abstract

Cellular senescence is the arrest of normal cell division. Oncogenic genes and oxidative stress, which cause genomic DNA damage and generation of reactive oxygen species, lead to cellular senescence. The senescence-associated secretory phenotype is a distinct feature of senescence. Senescence is normally involved in the embryonic development. Senescent cells can communicate with immune cells to invoke an immune response. Senescence emerges during the aging process in several tissues and organs. In fact, increasing evidence shows that cellular senescence is implicated in aging-related diseases, such as nonalcoholic fatty liver disease, obesity and diabetes, pulmonary hypertension, and tumorigenesis. Cellular senescence can also be induced by microbial infection. During cellular senescence, several signaling pathways, including those of p53, nuclear factor-κB (NF-κB), mammalian target of rapamycin, and transforming growth factor-beta, play important roles. Accumulation of senescent cells can trigger chronic inflammation, which may contribute to the pathological changes in the elderly. Given the variety of deleterious effects caused by cellular senescence in humans, strategies have been proposed to control senescence. In this review, we will focus on recent studies to provide a brief introduction to cellular senescence, including associated signaling pathways and pathology.

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Cardiac ageing: extrinsic and intrinsic factors in cellular renewal and senescence

Natalie A. Gude, Kathleen M. Broughton, Fareheh Firouzi & Mark A. Sussman

Cardiac ageing manifests as a decline in function leading to heart failure. At the cellular level, ageing entails decreased replicative capacity and dysregulation of cellular processes in myocardial and nonmyocyte cells. Various extrinsic parameters, such as lifestyle and environment, integrate important signalling pathways, such as those involving inflammation and oxidative stress, with intrinsic molecular mechanisms underlying resistance versus progression to cellular senescence. Mitigation of cardiac functional decline in an ageing organism requires the activation of enhanced maintenance and reparative capacity, thereby overcoming inherent endogenous limitations to retaining a youthful phenotype. Deciphering the molecular mechanisms underlying dysregulation of cellular function and renewal reveals potential interventional targets to attenuate degenerative processes at the cellular and systemic levels to improve quality of life for our ageing population. In this Review, we discuss the roles of extrinsic and intrinsic factors in cardiac ageing. Animal models of cardiac ageing are summarized, followed by an overview of the current and possible future treatments to mitigate the deleterious effects of cardiac ageing.

OTHER RESEARCH

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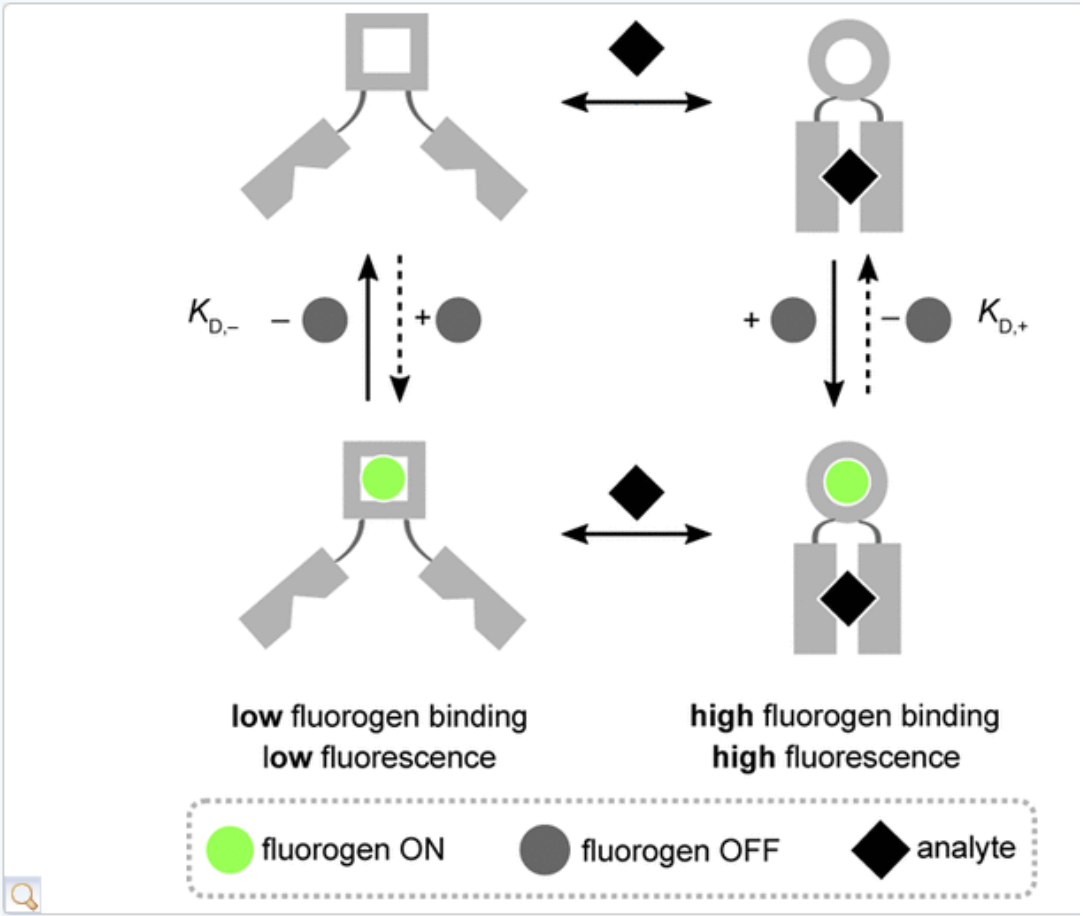
One in five genetics papers contains errors thanks to Microsoft Excel

By Jessica Boddy | Aug. 29, 2016 , 1:45 PM

Autoformatting in Microsoft Excel has caused many a headache—but now, a new study shows that one in five genetics papers in top scientific journals **contains errors from the program**, *The Washington Post* reports. The errors often arose when gene names in a spreadsheet **were automatically changed** to calendar dates or numerical values. For example, one gene called *Septin-2* is commonly shortened to *SEPT2*, but is changed to 2-SEP and stored as the date 2 September 2016 by Excel. The researchers, who published their analysis in *Genome Biology*, say the issue can be fixed by formatting Excel columns as text and remaining vigilant—or switching to Google Sheets, where gene names are stored exactly as they're entered.

Circularly Permuted Fluorogenic Proteins for the Design of Modular Biosensors



Fluorescent reporters are essential components for the design of optical biosensors that are able to image intracellular analytes in living cells. Herein, we describe the development of circularly permuted variants of Fluorescence-Activating and absorption-Shifting Tag (FAST) and demonstrate their potential as reporting module in biosensors. Circularly permutated FAST (cpFAST) variants allow one to condition the binding and activation of a fluorogenic ligand (and thus fluorescence) to analyte recognition by coupling them with analyte-binding domains. We demonstrated their use for biosensor design by generating multicolor plug-and-play fluorogenic biosensors for imaging the intracellular levels of Ca^{2+} in living mammalian cells in real time.

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CRISPR-guided DNA polymerases enable diversification of all nucleotides in a tunable window

The capacity to diversify genetic codes advances our ability to understand and engineer biological systems[1,2]. A method for continuously diversifying user-defined regions of a genome would enable forward genetic approaches in systems that are not amenable to efficient homology-directed oligonucleotide integration. It would also facilitate the rapid evolution of biotechnologically useful phenotypes through accelerated and parallelized rounds of mutagenesis and selection, as well as cell-lineage tracking through barcode mutagenesis. Here we present EvolvR, a system that can continuously diversify all nucleotides within a tunable window length at user-defined loci. This is achieved by directly generating mutations using engineered DNA polymerases targeted to loci via CRISPR-guided nickases. We identified nickase and polymerase variants that offer a range of targeted mutation rates that are up to 7,770,000-fold greater than rates seen in wild-type cells, and editing windows with lengths of up to 350 nucleotides. We used EvolvR to identify novel ribosomal mutations that confer resistance to the antibiotic spectinomycin. Our results demonstrate that CRISPR-guided DNA polymerases enable multiplexed and continuous diversification of user-defined genomic loci, which will be useful for a broad range of basic and biotechnological applications.

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An APOBEC3A-Cas9 base editor with minimized bystander and off-target activities

Base editor technology, which uses CRISPR–Cas9 to direct cytidine deaminase enzymatic activity to specific genomic loci, enables the highly efficient introduction of precise cytidine-to-thymidine DNA alterations[1,2,3,4,5,6]. However, existing base editors create unwanted C-to-T alterations when more than one C is present in the enzyme's five-base-pair editing window. Here we describe a strategy for reducing bystander mutations using an engineered human APOBEC3A (eA3A) domain, which preferentially deaminates cytidines in specific motifs according to a TCR>TCY>VCN hierarchy. In direct comparisons with the widely used base editor 3 (BE3) fusion in human cells, our eA3A-BE3 fusion exhibits similar activities on cytidines in TC motifs but greatly reduced editing on cytidines in other sequence contexts. eA3A-BE3 corrects a human β-thalassemia promoter mutation with much higher (>40-fold) precision than BE3. We also demonstrate that eA3A-BE3 shows reduced mutation frequencies on known off-target sites of BE3, even when targeting promiscuous homopolymeric sites.