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Scientific News
7th of February 2016
Sven Bulterijs

Initiative by Heales member Victor Björk

A Celebration Of The Oldest Person On Record: Calment's Day

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Naturally occurring $p16^{Ink4a}$-positive cells shorten healthy lifespan

Darren J. Baker, Bennett G. Childs, Matej Durik, Melinde E. Wijers, Cynthia J. Sieben, Jian Zhong, Rachel A. Saltness, Karthik B. Jeganathan, Grace Casaclang Verzosa, Abdulmohammad Pezeshki, Khashayarsha Khazaie, Jordan D. Miller & Jan M. van Deursen

Cellular senescence, a stress-induced irreversible growth arrest often characterized by expression of $p16^{Ink4a}$ (encoded by the *Ink4a/Arf* locus, also known as *Cdkn2a*) and a distinctive secretory phenotype, prevents the proliferation of preneoplastic cells and has beneficial roles in tissue remodelling during embryogenesis and wound healing. Senescent cells accumulate in various tissues and organs over time, and have been speculated to have a role in ageing. To explore the physiological relevance and consequences of naturally occurring senescent cells, here we use a previously established transgene, *INK-ATTAC*, to induce apoptosis in $p16^{Ink4a}$-expressing cells of wild-type mice by injection of AP20187 twice a week starting at one year of age. We show that compared to vehicle alone, AP20187 treatment extended median lifespan in both male and female mice of two distinct genetic backgrounds. The clearance of $p16^{Ink4a}$-positive cells delayed tumorigenesis and attenuated age-related deterioration of several organs without apparent side effects, including kidney, heart and fat, where clearance preserved the functionality of glomeruli, cardio-protective K_{ATP} channels and adipocytes, respectively. Thus, $p16^{Ink4a}$-positive cells that accumulate during adulthood negatively influence lifespan and promote age-dependent changes in several organs, and their therapeutic removal may be an attractive approach to extend healthy lifespan.

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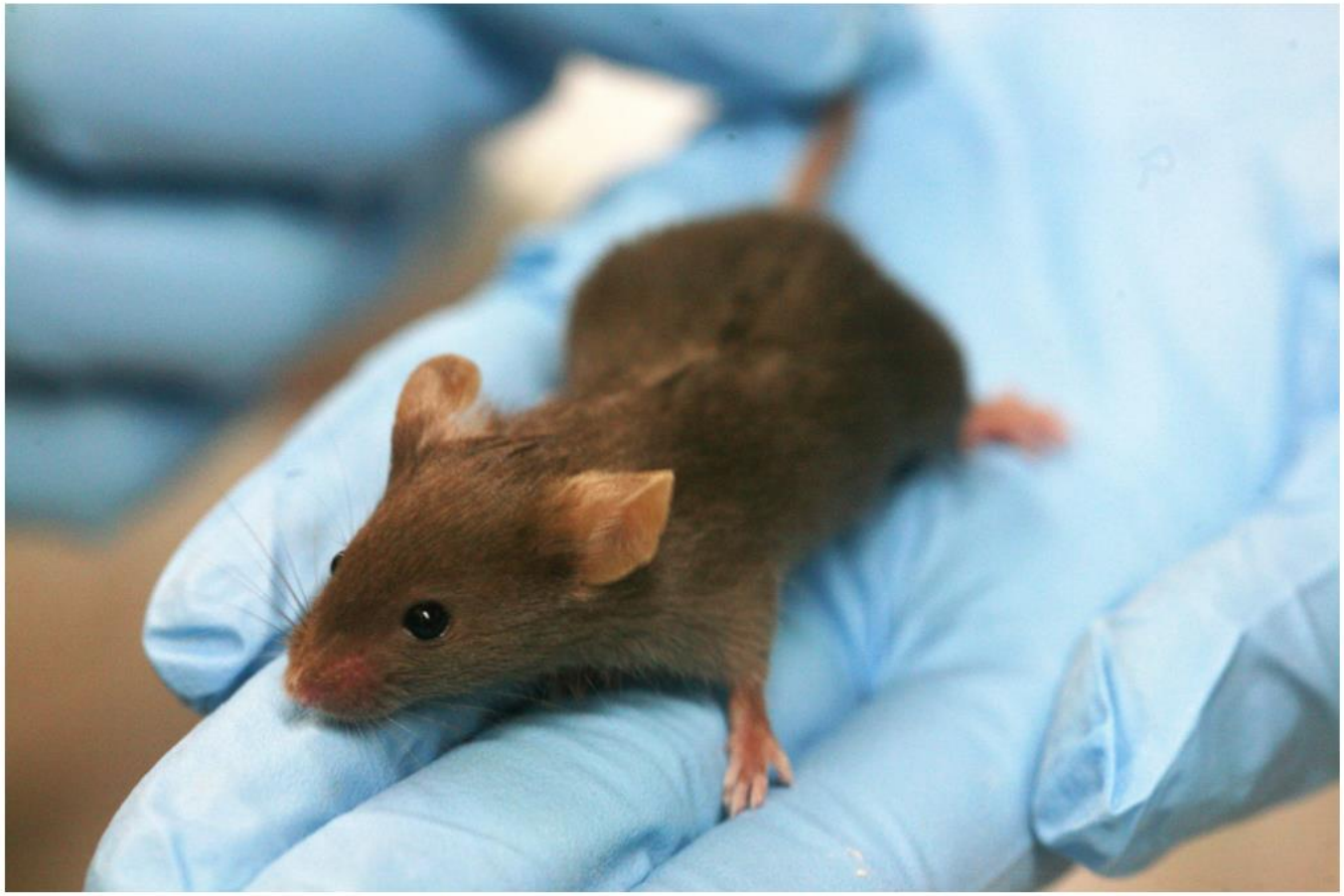
Eliminating Senescent Cells Increases Lifespan



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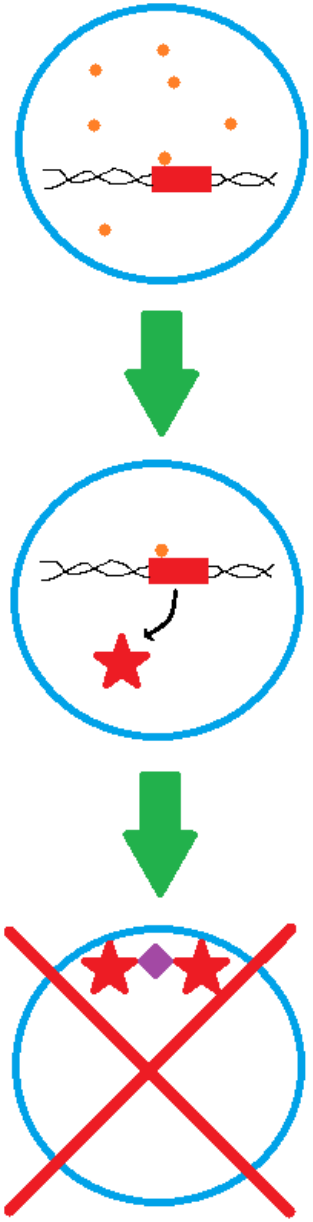
Senescent cell



1. Senescent cells produce high levels of p16

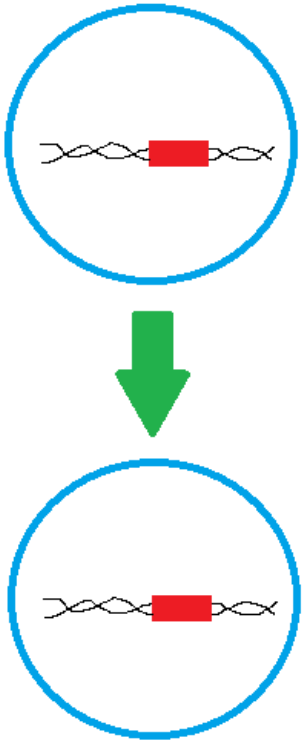
2. p16 binds to the suicide construct

3. This leads to the production of the suicide protein

4. In the presence of the drug this suicide protein is activated

5. The senescent cell dies

Normal cell



1. Normal cells have no increased levels of p16

2. Hence the suicide construct is not activated

3. No suicide protein is produced and the cell continues to live

p16

Genetic suicide construct

Suicide protein

Drug

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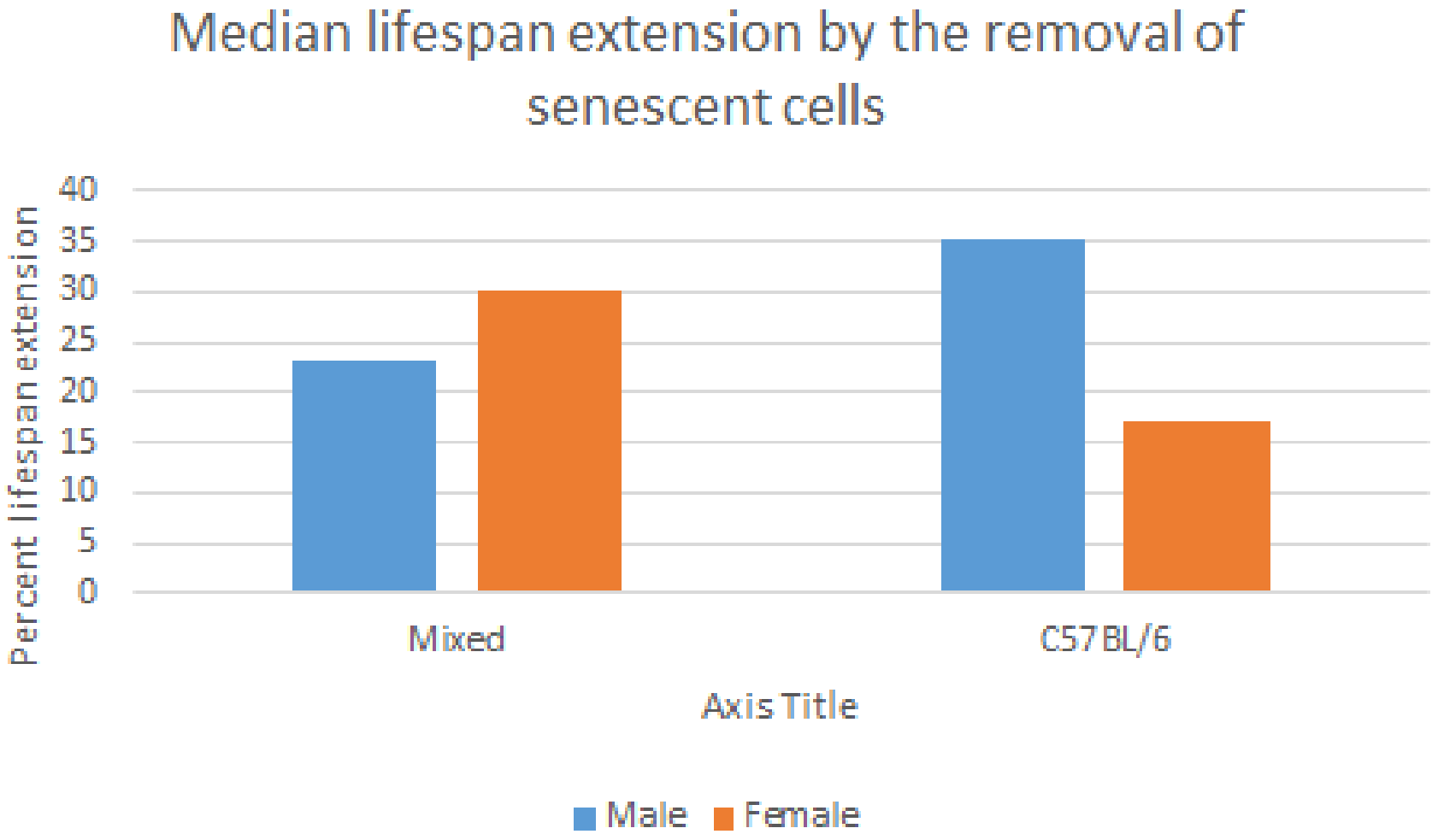

2 19 Tobias Wijshake

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Initial Case Reports of Cancer in Naked Mole-rats (*Heterocephalus glaber*)

1-6

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vet.sagepub.com

M. A. Delaney[1], J. M. Ward[2], T. F. Walsh[3], S. K. Chinnadurai[4], K. Kerns[3], M. J. Kinsel[5], and P. M. Treuting[1]

Abstract

Naked mole-rats (NMRs; *Heterocephalus glaber*) are highly adapted, eusocial rodents renowned for their extreme longevity and resistance to cancer. Because cancer has not been formally described in this species, NMRs have been increasingly utilized as an animal model in aging and cancer research. We previously reported the occurrence of several age-related diseases, including putative pre-neoplastic lesions, in zoo-housed NMR colonies. Here, we report for the first time 2 cases of cancer in zoo-housed NMRs. In Case No. 1, we observed a subcutaneous mass in the axillary region of a 22-year-old male NMR, with histologic, immunohistochemical (pancytokeratin positive, rare p63 immunolabeling, and smooth muscle actin negative), and ultrastructural characteristics of an adenocarcinoma possibly of mammary or salivary origin. In Case No. 2, we observed a densely cellular, poorly demarcated gastric mass of polygonal cells arranged in nests with positive immunolabeling for synaptophysin and chromogranin indicative of a neuroendocrine carcinoma in an approximately 20-year-old male NMR. We also include a brief discussion of other proliferative growths and pre-cancerous lesions diagnosed in 1 zoo colony. Although these case reports do not alter the longstanding observation of cancer resistance, they do raise questions about the scope of cancer resistance and the interpretation of biomedical studies in this model. These reports also highlight the benefit of long-term disease investigations in zoo-housed populations to better understand naturally occurring disease processes in species used as models in biomedical research.

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Amyloid-β pathology and cerebral amyloid angiopathy are frequent in iatrogenic Creutzfeldt-Jakob disease after dural grafting

QUESTIONS UNDER STUDY: Alzheimer-type amyloid-β (Aβ) pathology was reported in brains of individuals developing iatrogenic Creutzfeldt-Jakob disease (iCJD) after treatment with human cadaveric growth hormone, and interpreted as evidence of human transmission of Aβ by the treatment. Here we investigated the prevalence of Aβ pathology in other instances of iCJD related to dura mater grafts.

METHODS: By use of immunohistochemistry for Aβ, we investigated seven brains of patients (age range 28–63) who succumbed to iCJD after dural grafting, which had been applied by means of neurosurgery between 11 and 25 years before death. For control, we examined a series of 21 brains of age-matched (40–63 years) patients with sporadic CJD (sCJD) and an additional series of 81 sCJD cases (55–85 years) with the same methods.

RESULTS: In five of seven iCJD brains, Aβ was deposited in meningeal vessels as congophilic amyloid angiopathy and brain parenchymal plaques. This was significantly ($p < 0.001$) more frequent than in the age-matched sCJD controls and in the usual sCJD series.

CONCLUSIONS: We conclude that congophilic amyloid angiopathy and brain parenchymal Aβ plaques are frequent in iCJD after dural grafting. The presence of Aβ pathology in young individuals is highly unusual and suggests a causal relationship to the dural grafts. Further studies will be needed to elucidate whether such pathology resulted from the seeding of Aβ aggregates from the grafts to host tissues.

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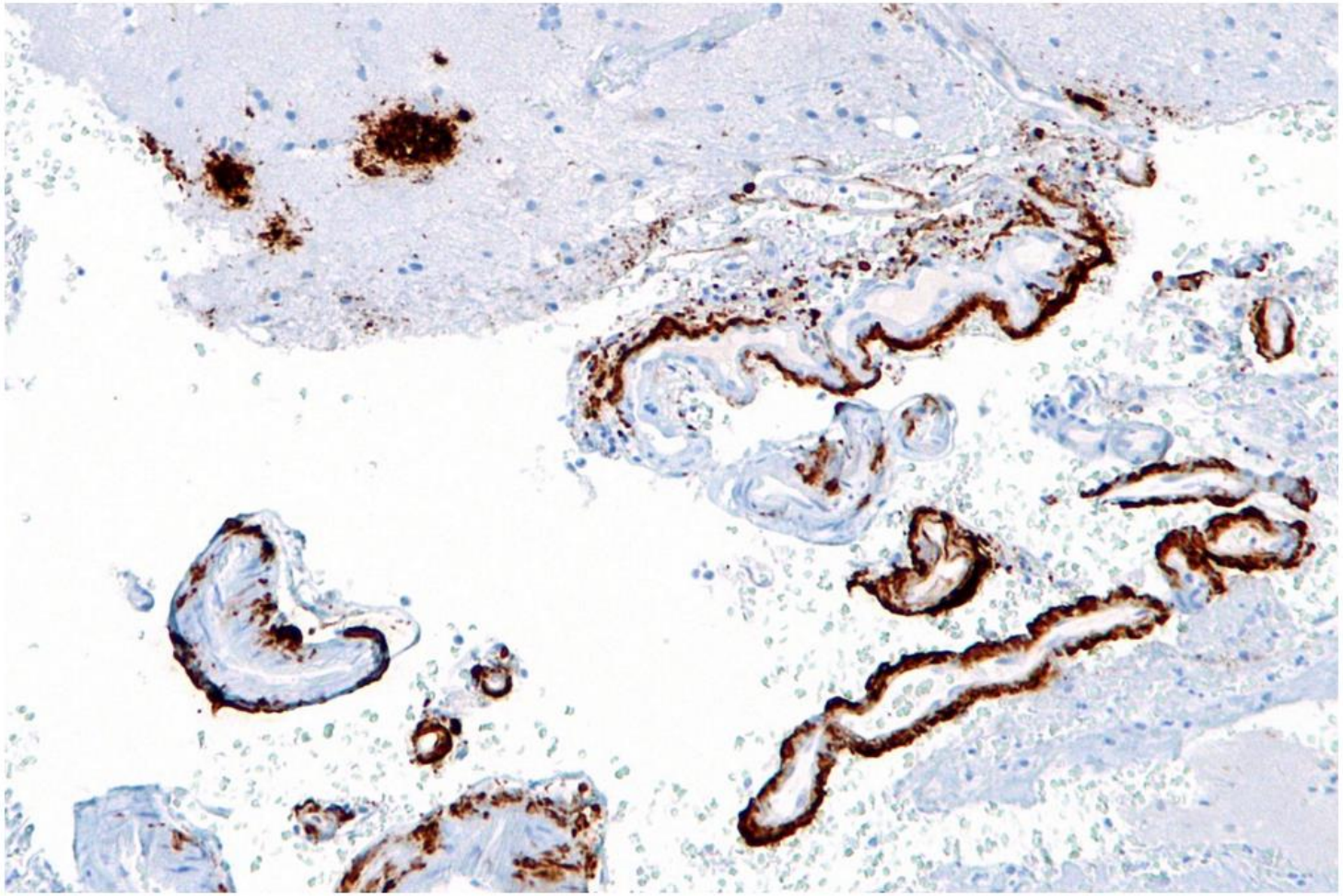
Is Alzheimer's An Infectious Disease?



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Free Radic Biol Med. 2016 Feb 1. pii: S0891-5849(16)00043-5. doi: 10.1016/j.freeradbiomed.2016.01.029. [Epub ahead of print]

Do glutathione levels decline in aging human brain?

Tong J[1], Fitzmaurice PS[2], Moszczynska A[3], Mattina K[4], Ang LC[5], Boileau I[6], Furukawa Y[7], Sailasuta N[8], Kish SJ[9].

Author information

Abstract

For the past 60 years a major theory of "aging" is that age-related damage is largely caused by excessive uncompensated oxidative stress. The ubiquitous tripeptide glutathione is a major antioxidant defence mechanism against reactive free radicals and has also served as a marker of changes in oxidative stress. Some (albeit conflicting) animal data suggest a loss of glutathione in brain senescence, which might compromise the ability of the aging brain to meet the demands of oxidative stress. Our objective was to establish whether advancing age is associated with glutathione deficiency in human brain. We measured reduced glutathione (GSH) levels in multiple regions of autopsied brain of normal subjects (n=74) aged one day to 99 years. Brain GSH levels during the infancy/teenage years were generally similar to those in the oldest examined adult group (76-99 years). During adulthood (23 to 99 years) GSH levels remained either stable (occipital cortex) or increased (caudate nucleus, frontal and cerebellar cortices). To the extent that GSH levels represent glutathione antioxidant capacity, our postmortem data suggest that human brain aging is not associated with declining glutathione status. We suggest that aged healthy human brains can maintain antioxidant capacity related to glutathione and that an age-related increase in GSH levels in some brain regions might possibly be a compensatory response to increased oxidative stress. Since our findings, although suggestive, suffer from the generic limitations of all postmortem brain studies, we also suggest the need for "replication" investigations employing the new ^{1}H MRS imaging procedures in living human brain.

KEYWORDS: Aging; Glutathione; Human brain; Oxidative stress; Postmortem

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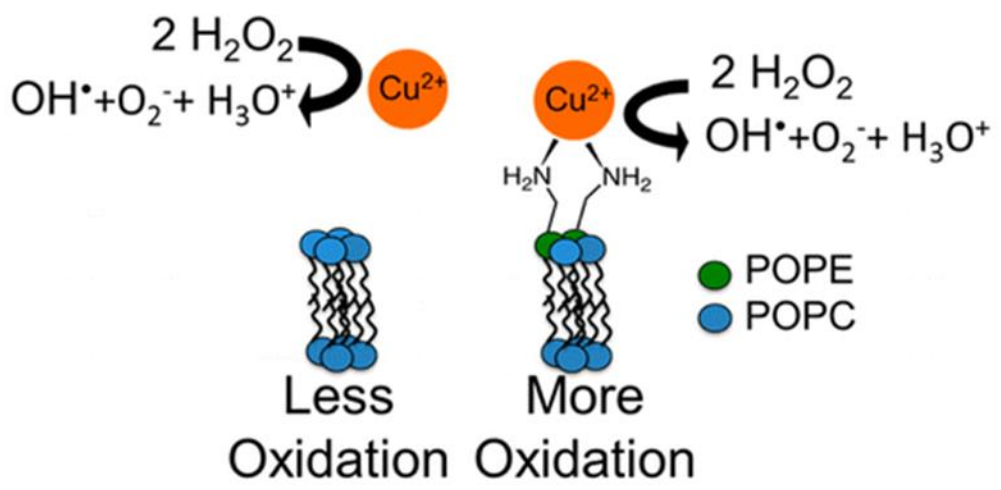
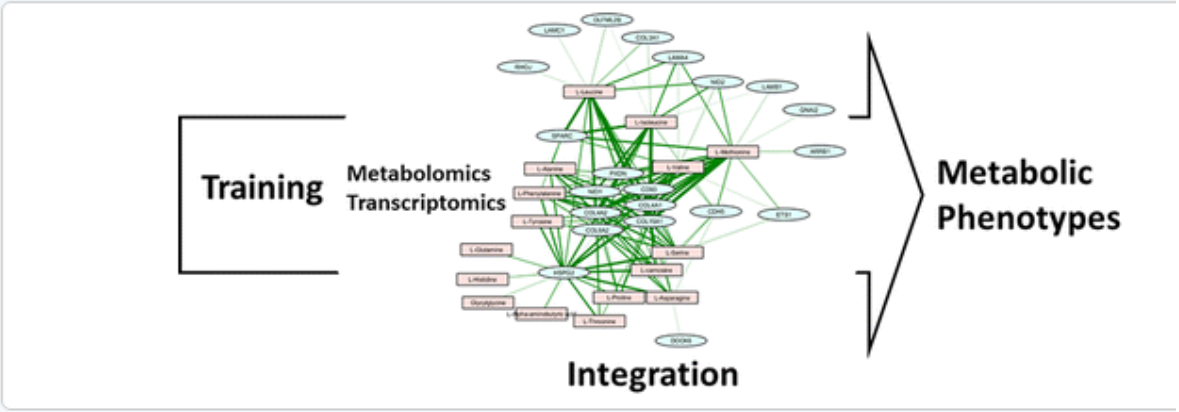
Cu^{2+} Binds to Phosphatidylethanolamine and Increases Oxidation in Lipid Membranes

Matthew F. Poyton†, Anne M. Sendecki†, Xiao Cong§, and Paul S. Cremer*†‡



Herein, we demonstrate that Cu^{2+} binds bivalently to phosphatidylethanolamine (PE), the second most abundant lipid in mammalian cells. The apparent equilibrium dissociation constant, K_{DApp}, for the Cu^{2+}–PE complex at physiological pH is approximately 2 μM and is insensitive to the concentration of PE in the membrane. By contrast, at pH 10.0, where PE lipids bear a negative charge, K_{DApp} decreases with increasing PE content and has a value of 150 nM for bilayers containing 70 mol % PE. The oxidation of double bonds in PE-containing bilayers can be monitored in the presence of Cu^{2+}. Strikingly, it was found that the oxidation rate is 8.2 times faster at pH 7.4 for bilayers containing 70 mol % PE than for pure phosphatidylcholine (PC) bilayers upon exposure of both to 70 μM Cu^{2+} and 10 mM hydrogen peroxide. The rate of oxidation increases linearly with the PE content in the membrane. These results may help explain the high level of lipid oxidation in PE-containing membranes for neurodegenerative diseases and autism where the Cu^{2+} concentration in the body is abnormally high.

The Muscle Metabolome Differs between Healthy and Frail Older Adults



Populations around the world are aging rapidly. Age-related loss of physiological functions negatively affects quality of life. A major contributor to the frailty syndrome of aging is loss of skeletal muscle. In this study we assessed the skeletal muscle biopsy metabolome of healthy young, healthy older and frail older subjects to determine the effect of age and frailty on the metabolic signature of skeletal muscle tissue. In addition, the effects of prolonged whole-body resistance-type exercise training on the muscle metabolome of older subjects were examined. The baseline metabolome was measured in muscle biopsies collected from 30 young, 66 healthy older subjects, and 43 frail older subjects. Follow-up samples from frail older (24 samples) and healthy older subjects (38 samples) were collected after 6 months of prolonged resistance-type exercise training. Young subjects were included as a reference group. Primary differences in skeletal muscle metabolite levels between young and healthy older subjects were related to mitochondrial function, muscle fiber type, and tissue turnover. Similar differences were observed when comparing frail older subjects with healthy older subjects at baseline. Prolonged resistance-type exercise training resulted in an adaptive response of amino acid metabolism, especially reflected in branched chain amino acids and genes related to tissue remodeling. The effect of exercise training on branched-chain amino acid-derived acylcarnitines in older subjects points to a downward shift in branched-chain amino acid catabolism upon training. We observed only modest correlations between muscle and plasma metabolite levels, which pleads against the use of plasma metabolites as a direct read-out of muscle metabolism and stresses the need for direct assessment of metabolites in muscle tissue biopsies.

Mortality in Individuals Treated With Glucose-Lowering Agents: A Large, Controlled Cohort Study

Patients:

A total of 115 896 patients starting metformin, sulfonylurea, or insulin (alone or in combination) between January 2003 and December 2007 participated in the study. Control subjects without GLA therapy were matched for age, gender, history of cardiovascular events, and therapy with antihypertensives, statins and blood platelet aggregation inhibitors.

Intervention(s):

There were no interventions.

Main Outcome Measure:

Five-year survival after the start of GLA was measured.

Results:

Profiles of patients using different GLAs varied, with patients on sulfonylurea being oldest and patients on insulin having more frequently a history of cardiovascular disease. Excess mortality differed across GLA therapies compared with matched controls without GLAs, even after adjusting for observable characteristics. Only metformin monotherapy was not associated with an increased 5-year mortality compared with matched controls, whereas individuals on a combination of sulfonylurea and insulin had the highest mortality risks. Age and concomitant use of statins strongly affect survival.

Conclusions:

Differences exist in 5-year survival of patients on GLA, at least partly driven by the risk profile of the individuals themselves. Metformin use was associated with lowest 5-year mortality risk and statins dramatically lowered 5-year mortality throughout all cohorts.

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Disentangling type 2 diabetes and metformin treatment signatures in the human gut microbiota

In recent years, several associations between common chronic human disorders and altered gut microbiome composition and function have been reported[1, 2]. In most of these reports, treatment regimens were not controlled for and conclusions could thus be confounded by the effects of various drugs on the microbiota, which may obscure microbial causes, protective factors or diagnostically relevant signals. Our study addresses disease and drug signatures in the human gut microbiome of type 2 diabetes mellitus (T2D). Two previous quantitative gut metagenomics studies of T2D patients that were unstratified for treatment yielded divergent conclusions regarding its associated gut microbial dysbiosis[3, 4]. Here we show, using 784 available human gut metagenomes, how antidiabetic medication confounds these results, and analyse in detail the effects of the most widely used antidiabetic drug metformin. We provide support for microbial mediation of the therapeutic effects of metformin through short-chain fatty acid production, as well as for potential microbiota-mediated mechanisms behind known intestinal adverse effects in the form of a relative increase in abundance of *Escherichia* species. Controlling for metformin treatment, we report a unified signature of gut microbiome shifts in T2D with a depletion of butyrate-producing taxa[3, 4]. These in turn cause functional microbiome shifts, in part alleviated by metformin-induced changes. Overall, the present study emphasizes the need to disentangle gut microbiota signatures of specific human diseases from those of medication.

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New Studies On Survival In Metformin Treated Diabetes Patients And Its Effect On The Microbiome

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Br J Nutr. 2016 Feb;115(4):629-36. doi: 10.1017/S0007114515004833.

Short-term effects of dietary advanced glycation end products in rats.

Poulsen MW[1], Andersen JM[1], Hedegaard RV[2], Madsen AN[3], Krath BN[1], Monošík R[1], Bak MJ[1], Nielsen J[4], Holst B[3], Skibsted LH[2], Larsen LH[1], Dragsted LO[1].

⊕ Author information

Abstract

Dietary advanced glycation end products (AGE) formed during heating of food have gained interest as potential nutritional toxins with adverse effects on inflammation and glucose metabolism. In the present study, we investigated the short-term effects of high and low molecular weight (HMW and LMW) dietary AGE on insulin sensitivity, expression of the receptor for AGE (RAGE), the AGE receptor 1 (AGER1) and TNF-α, F2-isoprostaglandins, body composition and food intake. For 2 weeks, thirty-six Sprague-Dawley rats were fed a diet containing 20 % milk powder with different proportions of this being given as heated milk powder (0, 40 or 100 %), either native (HMW) or hydrolysed (LMW). Gene expression of RAGE and AGER1 in whole blood increased in the group receiving a high AGE LMW diet, which also had the highest urinary excretion of the AGE, methylglyoxal-derived hydroimidazolone 1 (MG-H1). Urinary excretion of N ε -carboxymethyl-lysine increased with increasing proportion of heat-treated milk powder in the HMW and LMW diets but was unrelated to gene expression. There was no difference in insulin sensitivity, F2-isoprostaglandins, food intake, water intake, body weight or body composition between the groups. In conclusion, RAGE and AGER1 expression can be influenced by a high AGE diet after only 2 weeks in proportion to MG-H1 excretion. No other short-term effects were observed.

KEYWORDS: AGE advanced glycation end products; AGER1 gene for advanced glycation end product receptor 1; Advanced glycation end products; Body composition; CEL Nε -carboxyethyl-lysine; CML Nε -carboxymethyl-lysine; Gene expression; Gene for advanced glycation end product receptor 1; Gene for receptor for advanced glycation end products; H-AGE high advanced glycation end product; HMW high molecular weight; Insulin sensitivity; L-AGE low advanced glycation end product; LMW low molecular weight; MG-H1 methylglyoxal-derived hydroimidazolone-1; RAGE gene for receptor for advanced glycation end products; Rats

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The temporal scaling of *Caenorhabditis elegans* ageing

The process of ageing makes death increasingly likely, involving a random aspect that produces a wide distribution of lifespan even in homogeneous populations[1, 2]. The study of this stochastic behaviour may link molecular mechanisms to the ageing process that determines lifespan. Here, by collecting high-precision mortality statistics from large populations, we observe that interventions as diverse as changes in diet, temperature, exposure to oxidative stress, and disruption of genes including the heat shock factor *hsf-1*, the hypoxia-inducible factor *hif-1*, and the insulin/IGF-1 pathway components *daf-2*, *age-1*, and *daf-16* all alter lifespan distributions by an apparent stretching or shrinking of time. To produce such temporal scaling, each intervention must alter to the same extent throughout adult life all physiological determinants of the risk of death. Organismic ageing in *Caenorhabditis elegans* therefore appears to involve aspects of physiology that respond in concert to a diverse set of interventions. In this way, temporal scaling identifies a novel state variable, $r(t)$, that governs the risk of death and whose average decay dynamics involves a single effective rate constant of ageing, k_r. Interventions that produce temporal scaling influence lifespan exclusively by altering k_r. Such interventions, when applied transiently even in early adulthood, temporarily alter k_r with an attendant transient increase or decrease in the rate of change in r and a permanent effect on remaining lifespan. The existence of an organismal ageing dynamics that is invariant across genetic and environmental contexts provides the basis for a new, quantitative framework for evaluating the manner and extent to which specific molecular processes contribute to the aspect of ageing that determines lifespan.

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PLoS Genet. 2016 Jan 20;12(1):e1005798. doi: 10.1371/journal.pgen.1005798. eCollection 2016.

Short Telomeres in Key Tissues Initiate Local and Systemic Aging in Zebrafish.

Carneiro MC[1], Henriques CM[1], Nabais J[1], Ferreira T[1], Carvalho T[1], Ferreira MG[1].

⊕ Author information

Abstract

Telomeres shorten with each cell division and telomere dysfunction is a recognized hallmark of aging. Tissue proliferation is expected to dictate the rate at which telomeres shorten. We set out to test whether proliferative tissues age faster than non-proliferative due to telomere shortening during zebrafish aging. We performed a prospective study linking telomere length to tissue pathology and disease. Contrary to expectations, we show that telomeres shorten to critical lengths only in specific tissues and independently of their proliferation rate. Short telomeres accumulate in the gut but not in other highly proliferative tissues such as the blood and gonads. Notably, the muscle, a low proliferative tissue, accumulates short telomeres and DNA damage at the same rate as the gut. Together, our work shows that telomere shortening and DNA damage in key tissues triggers not only local dysfunction but also anticipates the onset of age-associated diseases in other tissues, including cancer.

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Preferential sites for intramolecular glucosepane cross-link formation in type I collagen: A thermodynamic study

The extracellular matrix (ECM) undergoes progressive age-related stiffening and loss of proteolytic digestibility due to an increase in concentration of advanced glycation end products (AGEs). The most abundant AGE, glucosepane, accumulates in collagen with concentrations over 100 times greater than all other AGEs. Detrimental collagen stiffening properties are believed to play a significant role in several age-related diseases such as osteoporosis and cardiovascular disease. Currently little is known of the potential location of covalently cross-linked glucosepane formation within collagen molecules; neither are there reports on how the respective cross-link sites affect the physical and biochemical properties of collagen. Using fully atomistic molecular dynamics simulations (MD) we have identified six sites where the formation of a covalent intra-molecular glucosepane cross-link within a single collagen molecule in a fibrillar environment is energetically favourable. Identification of these favourable sites enables us to align collagen cross-linking with experimentally observed changes to the ECM. For example, formation of glucosepane was found to be energetically favourable within close proximity of the Matrix Metalloproteinase-1 (MMP1) binding site, which could potentially disrupt collagen degradation.

ACS Chem Neurosci. 2016 Feb 1. [Epub ahead of print]

Synthesis and Evaluation of [18F]RAGER: A First Generation Small-Molecule PET Radioligand Targeting the Receptor for Advanced Glycation Endproducts.

Cary BP[1], Brooks AF[1], Fawaz MV[1,2], Drake LR[2], Desmond TJ[1], Sherman P[1], Quesada CA[1], Scott PJ[1,2].

Author information

Abstract

The receptor for advanced glycation endproducts (RAGE) is a 35 kDa transmembrane receptor that belongs to the immunoglobulin superfamily of cell surface molecules. Its role in Alzheimer's disease (AD) is complex, but it is thought to mediate influx of circulating amyloid-β into the brain as well as amplify Aβ-induced pathogenic responses. RAGE is therefore of considerable interest as both a diagnostic and a therapeutic target in AD. Herein we report the synthesis and preliminary preclinical evaluation of [^{18}F]RAGER, the first small molecule PET radiotracer for RAGE (K_d = 15 nM). Docking studies proposed a likely binding interaction between RAGE and RAGER, [^{18}F]RAGER autoradiography showed colocalization with RAGE identified by immunohistochemistry in AD brain samples, and [^{18}F]RAGER microPET confirmed CNS penetration and increased uptake in areas of the brain known to express RAGE. This first generation radiotracer represents initial proof-of-concept and a promising first step toward quantifying CNS RAGE activity using PET. However, there were high levels of nonspecific [^{18}F]RAGER binding in vitro, likely due to its high log P (experimental log P = 3.5), and rapid metabolism of [^{18}F]RAGER in rat liver microsome studies. Therefore, development of second generation ligands with improved imaging properties would be advantageous prior to anticipated translation into clinical PET imaging studies.

Chem Res Toxicol. 2016 Jan 27. [Epub ahead of print]

Metformin Scavenges Methylglyoxal To Form a Novel Imidazolinone Metabolite in Humans.

Kinsky OR[1], Hargraves TL[1], Anumol T[1], Jacobsen NE[1], Dai J[1], Snyder SA[1], Monks TJ[1], Lau SS[1].

Author information

Abstract

Methylglyoxal (MG) is a highly reactive dicarbonyl compound involved in the formation of advanced glycation endproducts (AGE). Levels of MG are elevated in patients with type-2 diabetes mellitus (T2DM), and AGE have been implicated in the progression of diabetic complications. The antihyperglycemic drug metformin (MF) has been suggested to be a scavenger of MG. The present work examined and characterized unequivocally the resulting scavenged product from the metformin-MG reaction. The primary product was characterized by ^{1}H, ^{13}C, 2D-HSQC, and HMBC NMR and tandem mass spectrometry. X-ray diffraction analysis determined the structure of the metformin and MG-derived imidazolinone compound as (E)-1,1-dimethyl-2-(5-methyl-4-oxo-4,5-dihydro-1H-imidazol-2-yl)guanidine (IMZ). A LC-MS/MS multiple reaction monitoring method was developed to detect and quantify the presence of IMZ in metformin-treated T2DM patients. Urine from >90 MF-treated T2DM patients was analyzed, with increased levels of MF directly correlating with elevations in IMZ. Urinary MF was detected in the range of 0.17 μM to 23.0 mM, and simultaneous measurement of IMZ concentrations were in the range of 18.8 nM to 4.3 μM. Since plasma concentrations of MG range from 40 nM to 4.5 μM, the level of IMZ production may be of therapeutic significance. Thus, in addition to lowering hepatic gluconeogenesis, metformin also scavenges the highly reactive MG in vivo, thereby reducing potentially detrimental MG protein adducts, with subsequent reductions in diabetic complications.

REVIEWS/COMMENTS/EDITORIALS

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Rejuvenation Res. 2015 Dec 9. [Epub ahead of print]

Whole-body Induced Cell Turnover: A proposed intervention for age-related damage and associated pathology.

Cortese FA[1], Santostasi G[2].

Author information

Abstract

In both biomedicine in general and biomedical gerontology in particular, cell replacement therapy is traditionally proposed as an intervention for cell loss. This paper presents a proposed intervention - Whole-body Induced Cell Turnover (WICT) - for use in biomedical gerontology that combines cell replacement therapy with a second therapeutic component so as to broaden the therapeutic utility of cell therapies and increase the categories of age-related damage that are amenable to cell-based interventions. In particular, WICT may allow cell therapies to serve as an intervention for accumulated cellular and intracellular damage, such as telomere depletion, gDNA and mtDNA damage and mutations, replicative senescence, functionally-deleterious age-related changes in gene expression, accumulated cellular and intracellular aggregates and functionally-deleterious post-translationally modified gene products. WICT consists of the gradual ablation and subsequent replacement of a patient's entire set of constituent cells gradually over the course of their adult lifespan via the quantitative and qualitative coordination of targeted cell ablation with exogenous cell administration. The aim is to remove age-associated cellular and intracellular damage present in the patient's endogenous cells. Here we outline the underlying techniques and technologies by which WICT can be mediated, describe the mechanisms by which it can serve to negate or prevent age-related cellular and intracellular damage, explicate the unique therapeutic components and utilities that distinguish it as a distinct type of cell-based intervention for use in biomedical gerontology and address potential complications associated with the therapy.

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Cold Spring Harb Perspect Med. 2016 Jan 8;6(2). pii: a025940. doi: 10.1101/cshperspect.a025940.

Articulating the Case for the Longevity Dividend.

Olshansky SJ[1].

Author information

Abstract

The survival of large segments of human populations to advanced ages is a crowning achievement of improvements in public health and medicine. But, in the 21st century, our continued desire to extend life brings forth a unique dilemma. The risk of death from cardiovascular diseases and many forms of cancer have declined, but even if they continue to do so in the future, the resulting health benefits and enhanced longevities are likely to diminish. It is even possible that healthy life expectancy could decline in the future as major fatal diseases wane. The reason is that the longer we live, the greater is the influence of biological aging on the expression of fatal and disabling diseases. As long as the rates of aging of our bodies continues without amelioration, the progress we make on all major disease fronts must eventually face a point of diminishing returns. Research in the scientific study of aging has already showed that the aging of our bodies is inherently modifiable, and that a therapeutic intervention that slows aging in people is a plausible target for science and public health. Given the speed with which population aging is progressing and chronic fatal and disabling conditions are challenging health care costs across the globe, the case is now being made in the scientific literature that delayed aging could be one of the most efficient and promising ways to combat disease, extend healthy life, compress morbidity, and reduce health care costs. A consortium of scientists and nonprofit organizations has devised a plan to initiate an accelerated program of scientific research to develop, test for safety and efficacy, and then disseminate a therapeutic intervention to delay aging if proven to be safe and effective; this is referred to as the Longevity Dividend Initiative Consortium (LDIC). In this review, I articulate the case for the LDIC.