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Scientific News
1st of July 2018
Sven Bulterijs

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- Marco Demaria
- Andrea Ablasser
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- Björn Schumacher
- Guido Kroemer
- Georg Füllen
- Andrea Maier
- Aubrey de Grey
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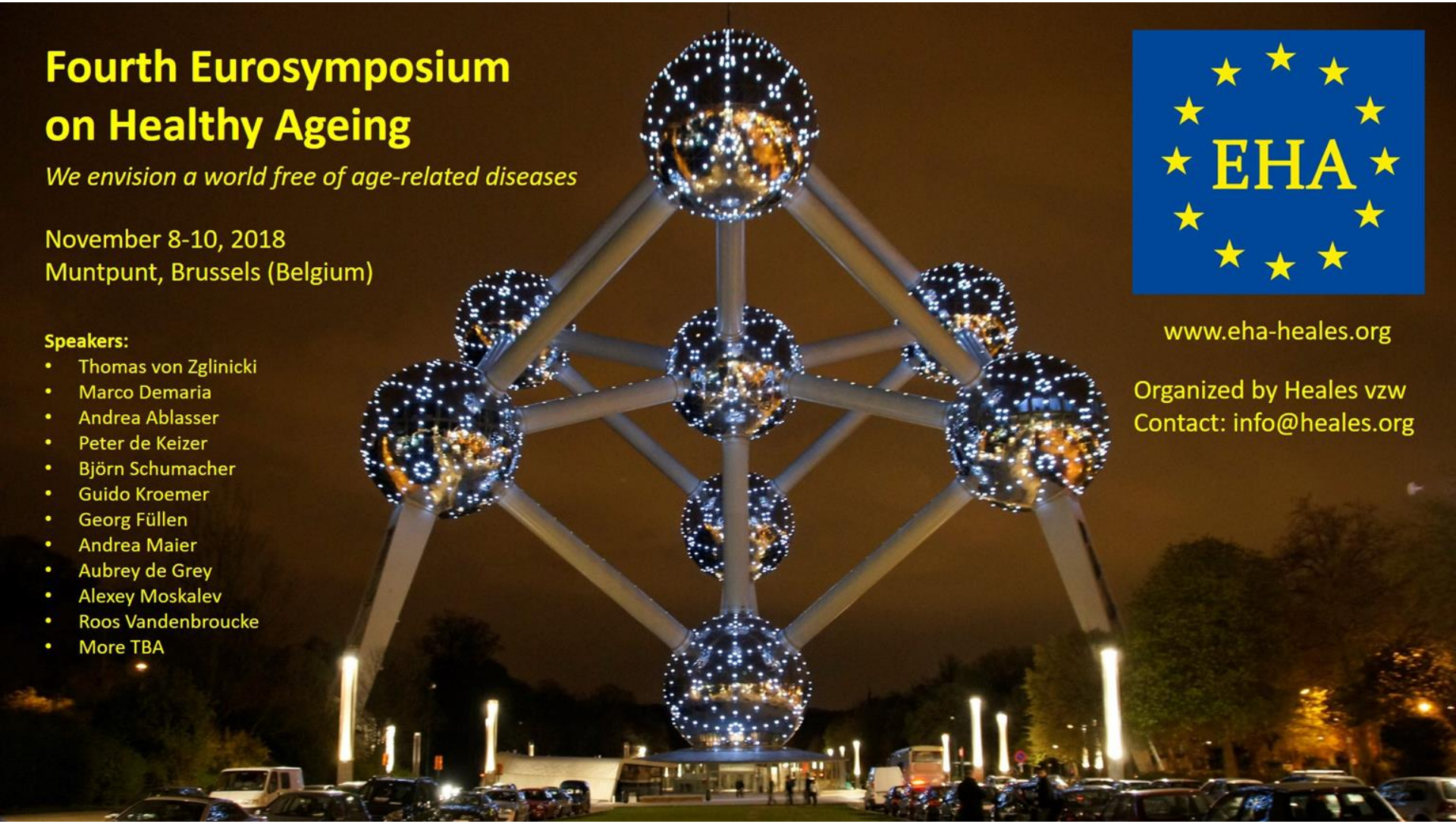

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AbbVie and Calico renew their aging research collaboration with an extra $1B

by Conor Hale | Jun 26, 2018 9:55am

Since the collaboration got underway in 2014, researchers have produced more than two dozen early-stage programs in oncology and neuroscience, which Calico plans to advance into early-phase trials over the coming years. (AbbVie)

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The plateau of human mortality: Demography of longevity pioneers

Elisabetta Barbi[1,*], Francesco Lagona[2], Marco Marsili[3], James W. Vaupel[4,5,6,7], Kenneth W. Wachter[8]

Theories about biological limits to life span and evolutionary shaping of human longevity depend on facts about mortality at extreme ages, but these facts have remained a matter of debate. Do hazard curves typically level out into high plateaus eventually, as seen in other species, or do exponential increases persist? In this study, we estimated hazard rates from data on all inhabitants of Italy aged 105 and older between 2009 and 2015 (born 1896–1910), a total of 3836 documented cases. We observed level hazard curves, which were essentially constant beyond age 105. Our estimates are free from artifacts of aggregation that limited earlier studies and provide the best evidence to date for the existence of extreme-age mortality plateaus in humans.

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An evolutionary transcriptomics approach links CD36 to membrane remodeling in replicative senescence

Check for updates

Marie Saitou, Darleny Y Lizardo, Recep Ozgur Taskent, Alec Millner, Omer Gokcumen and Gunes Ekin Atilla-Gokcumen

Abstract

Cellular senescence, the irreversible ceasing of cell division, has been associated with organismal aging, prevention of cancerogenesis, and developmental processes. As such, the evolutionary basis and biological features of cellular senescence remain a fascinating area of research. In this study, we conducted comparative RNAseq experiments to detect genes associated with replicative senescence in two different human fibroblast cell lines and at different time points. We identified 841 and 900 genes (core senescence-associated genes) that are significantly up- and downregulated in senescent cells, respectively, in both cell lines. Our functional enrichment analysis showed that downregulated core genes are primarily involved in cell cycle processes while upregulated core gene enrichment indicated various lipid-related processes. We further demonstrated that downregulated genes are significantly more conserved than upregulated genes. Using both transcriptomics and genetic variation data, we identified one of the upregulated, lipid metabolism genes, CD36, as an outlier. We found that overexpression of CD36 induces a senescence-like phenotype and, further, the media of CD36-overexpressing cells alone can induce a senescence-like phenotype in proliferating young cells. Moreover, we used a targeted lipidomics approach and showed that phosphatidylcholines accumulate during replicative senescence in these cells, suggesting that upregulation of CD36 could contribute to membrane remodeling during senescence. Overall, these results contribute to the understanding of evolution and biology of cellular senescence and identify several targets and questions for future studies.

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JAMA Cardiol. 2018 Jun 20. doi: 10.1001/jamacardio.2018.1470. [Epub ahead of print]

Association of LPA Variants With Risk of Coronary Disease and the Implications for Lipoprotein(a)-Lowering Therapies: A Mendelian Randomization Analysis.

Burgess S[1,2], Ference BA[2,3,4], Staley JR[2,5], Freitag DF[2], Mason AM[2], Nielsen SF[6,7,8], Willeit P[2,9], Young R[2,10], Surendran P[2], Karthikeyan S[2], Bolton TR[2], Peters JE[2], Kamstrup PR[6,7], Tybjærg-Hansen A[7,8,11,12], Benn M[7,8,11], Langsted A[6,7], Schnohr P[12], Vedel-Krogh S[6,7,8], Kobylecki CJ[6,7,8], Ford I[10], Packard C[13], Trompet S[14,15], Jukema JW[14,16], Sattar N[13], Di Angelantonio E[2,17], Saleheen D[18,19], Howson JMM[2], Nordestgaard BG[6,7,8,12], Butterworth AS[2,17], Danesh J[2,17,20]; European Prospective Investigation Into Cancer and Nutrition–Cardiovascular Disease (EPIC-CVD) Consortium.

⊕ Author information

Abstract

IMPORTANCE: Human genetic studies have indicated that plasma lipoprotein(a) (Lp[a]) is causally associated with the risk of coronary heart disease (CHD), but randomized trials of several therapies that reduce Lp(a) levels by 25% to 35% have not provided any evidence that lowering Lp(a) level reduces CHD risk.

OBJECTIVE: To estimate the magnitude of the change in plasma Lp(a) levels needed to have the same evidence of an association with CHD risk as a 38.67-mg/dL (ie, 1-mmol/L) change in low-density lipoprotein cholesterol (LDL-C) level, a change that has been shown to produce a clinically meaningful reduction in the risk of CHD.

DESIGN, SETTING, AND PARTICIPANTS: A mendelian randomization analysis was conducted using individual participant data from 5 studies and with external validation using summarized data from 48 studies. Population-based prospective cohort and case-control studies featured 20 793 individuals with CHD and 27 540 controls with individual participant data, whereas summarized data included 62 240 patients with CHD and 127 299 controls. Data were analyzed from November 2016 to March 2018.

EXPOSURES: Genetic LPA score and plasma Lp(a) mass concentration.

MAIN OUTCOMES AND MEASURES: Coronary heart disease.

RESULTS: Of the included study participants, 53% were men, all were of white European ancestry, and the mean age was 57.5 years. The association of genetically predicted Lp(a) with CHD risk was linearly proportional to the absolute change in Lp(a) concentration. A 10-mg/dL lower genetically predicted Lp(a) concentration was associated with a 5.8% lower CHD risk (odds ratio [OR], 0.942; 95% CI, 0.933-0.951; P = 3 × 10-37), whereas a 10-mg/dL lower genetically predicted LDL-C level estimated using an LDL-C genetic score was associated with a 14.5% lower CHD risk (OR, 0.855; 95% CI, 0.818-0.893; P = 2 × 10-12). Thus, a 101.5-mg/dL change (95% CI, 71.0-137.0) in Lp(a) concentration had the same association with CHD risk as a 38.67-mg/dL change in LDL-C level. The association of genetically predicted Lp(a) concentration with CHD risk appeared to be independent of changes in LDL-C level owing to genetic variants that mimic the relationship of statins, PCSK9 inhibitors, and ezetimibe with CHD risk.

CONCLUSIONS AND RELEVANCE: The clinical benefit of lowering Lp(a) is likely to be proportional to the absolute reduction in Lp(a) concentration. Large absolute reductions in Lp(a) of approximately 100 mg/dL may be required to produce a clinically meaningful reduction in the risk of CHD similar in magnitude to what can be achieved by lowering LDL-C level by 38.67 mg/dL (ie, 1 mmol/L).

Anti-Inflammatory Therapy With Canakinumab for the Prevention and Management of Diabetes

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Methods

The authors randomized 10,061 patients with prior myocardial infarction and high-sensitivity C-reactive protein (hsCRP) ≥2 mg/l to placebo or canakinumab at doses of 50 mg, 150 mg, or 300 mg subcutaneously once every 3 months. The authors tested the effects of canakinumab on major cardiovascular events in patients with and without diabetes at baseline, and evaluated as a pre-specified analysis whether canakinumab would reduce the risk of adjudicated cases of new-onset type 2 diabetes among those with protocol-defined pre-diabetes at trial entry. The authors also evaluated the effect of canakinumab on fasting plasma glucose and glycosylated hemoglobin (HbA_{1c}) in patients with and without established diabetes.

Results

Of the participants, 4,057 (40.3%) had baseline diabetes, 4,960 (49.3%) had pre-diabetes, and 1,044 (10.4%) had normal glucose levels. Among those without diabetes, increasing tertiles of hsCRP at baseline associated with an increased risk of developing diabetes during the median follow-up period of 3.7 years (incidence rates 3.2, 4.1, and 4.4 per 100 person-years; p = 0.003). Canakinumab 150 mg as compared with placebo had similar magnitude effects on major cardiovascular event rates among those with diabetes (hazard ratio [HR]: 0.85; 95% confidence interval [CI]: 0.70 to 1.03), pre-diabetes (HR: 0.86; 95% CI: 0.70 to 1.06), and normoglycemia (HR: 0.81; 95% CI: 0.49 to 1.35). Despite large reductions in hsCRP and IL-6, canakinumab did not reduce the incidence of new-onset diabetes, with rates per 100 person-years in the placebo, 50 mg, 150 mg, and 300 mg canakinumab groups of 4.2, 4.2, 4.4, and 4.1, respectively (log-rank p = 0.84). The HR comparing all canakinumab doses to placebo was 1.02 (95% CI: 0.87 to 1.19; p = 0.82). Canakinumab reduced HbA_{1c} during the first 6 to 9 months of treatment, but no consistent long-term benefits on HbA_{1c} or fasting plasma glucose were observed.

Conclusions

Although IL-1β inhibition with canakinumab had similar effects on major cardiovascular events among those with and without diabetes, treatment over a median period of 3.7 years did not reduce incident diabetes. (Canakinumab Anti-inflammatory Thrombosis Outcomes Study [CANTOS]; NCT01327846)

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Boosting ATM activity alleviates aging and extends lifespan in a mouse model of progeria

DNA damage accumulates with age (Lombard et al., 2005). However, whether and how robust DNA repair machinery promotes longevity is elusive. Here, we demonstrate that ATM-centered DNA damage response (DDR) progressively declines with senescence and age, while low dose of chloroquine (CQ) activates ATM, promotes DNA damage clearance, rescues age-related metabolic shift, and prolongs replicative lifespan. Molecularly, ATM phosphorylates SIRT6 deacetylase and thus prevents MDM2-mediated ubiquitination and proteasomal degradation. Extra copies of *Sirt6* extend lifespan in *Atm-/-* mice, with restored metabolic homeostasis. Moreover, the treatment with CQ remarkably extends lifespan of *Caenorhabditis elegans*, but not the *ATM-1* mutants. In a progeria mouse model with low DNA repair capacity, long-term administration of CQ ameliorates premature aging features and extends lifespan. Thus, our data highlights a pro-longevity role of ATM, for the first time establishing direct causal links between robust DNA repair machinery and longevity, and providing therapeutic strategy for progeria and age-related metabolic diseases.

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Late-life targeting of the IGF-1 receptor improves healthspan and lifespan in female mice

Diminished growth factor signaling improves longevity in laboratory models, while a reduction in the somatotropic axis is favorably linked to human aging and longevity. Given the conserved role of this pathway on lifespan, therapeutic strategies, such as insulin-like growth factor-1 receptor (IGF-1R) monoclonal antibodies (mAb), represent a promising translational tool to target human aging. To this end, we performed a preclinical study in 18-mo-old male and female mice treated with vehicle or an IGF-1R mAb (L2-Cmu, Amgen Inc), and determined effects on aging outcomes. Here we show that L2-Cmu preferentially improves female healthspan and increases median lifespan by 9% ($P = 0.03$) in females, along with a reduction in neoplasms and inflammation ($P \leq 0.05$). Thus, consistent with other models, targeting IGF-1R signaling appears to be most beneficial to females. Importantly, these effects could be achieved at advanced ages, suggesting that IGF-1R mAbs could represent a promising therapeutic candidate to delay aging.

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Postnatal Exocrine Pancreas Growth by Cellular Hypertrophy Correlates with a Shorter Lifespan in Mammals

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Developmental processes in different mammals are thought to share fundamental cellular mechanisms. We report a dramatic increase in cell size during postnatal pancreas development in rodents, accounting for much of the increase in organ size after birth. Hypertrophy of pancreatic acinar cells involves both higher ploidy and increased biosynthesis per genome copy; is maximal adjacent to islets, suggesting endocrine to exocrine communication; and is partly driven by weaning-related processes. In contrast to the situation in rodents, pancreas cell size in humans remains stable postnatally, indicating organ growth by pure hyperplasia. Pancreatic acinar cell volume varies 9-fold among 24 mammalian species analyzed, and shows a striking inverse correlation with organismal lifespan. We hypothesize that cellular hypertrophy is a strategy for rapid postnatal tissue growth, entailing life-long detrimental effects.

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J Biol Chem. 2018 Jun 22;293(25):9580-9593. doi: 10.1074/jbc.RA117.000499. Epub 2018 Apr 26.

Comparative analysis of Parkinson's disease-associated genes in mice reveals altered survival and bioenergetics of Parkin-deficient dopamine neurons.

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⊕ Author information

Abstract

Many mutations in genes encoding proteins such as Parkin, PTEN-induced putative kinase 1 (PINK1), protein deglycase DJ-1 (DJ-1 or PARK7), leucine-rich repeat kinase 2 (LRRK2), and α-synuclein have been linked to familial forms of Parkinson's disease (PD). The consequences of these mutations, such as altered mitochondrial function and pathological protein aggregation, are starting to be better understood. However, little is known about the mechanisms explaining why alterations in such diverse cellular processes lead to the selective loss of dopamine (DA) neurons in the substantia nigra (SNc) in the brain of individuals with PD. Recent work has shown that one of the reasons for the high vulnerability of SNc DA neurons is their high basal rate of mitochondrial oxidative phosphorylation (OXPHOS), resulting from their highly complex axonal arborization. Here, we examined whether axonal growth and basal mitochondrial function are altered in SNc DA neurons from Parkin-, Pink1-, or DJ-1-KO mice. We provide evidence for increased basal OXPHOS in Parkin-KO DA neurons and for reduced survival of DA neurons that have a complex axonal arbor. The surviving smaller neurons exhibited reduced vulnerability to the DA neurotoxin and mitochondrial complex I inhibitor MPP+, and this reduction was associated with reduced expression of the DA transporter. Finally, we found that glial cells play a role in the reduced resilience of DA neurons in these mice and that WT Parkin overexpression rescues this phenotype. Our results provide critical insights into the complex relationship between mitochondrial function, axonal growth, and genetic risk factors for PD.

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Neuromelanin organelles are specialized autolysosomes that accumulate undegraded proteins and lipids in aging human brain and are likely involved in Parkinson's disease

During aging, neuronal organelles filled with neuromelanin (a dark-brown pigment) and lipid bodies accumulate in the brain, particularly in the substantia nigra, a region targeted in Parkinson's disease. We have investigated protein and lipid systems involved in the formation of these organelles and in the synthesis of the neuromelanin of human substantia nigra. Membrane and matrix proteins characteristic of lysosomes were found in neuromelanin-containing organelles at a lower number than in typical lysosomes, indicating a reduced enzymatic activity and likely impaired capacity for lysosomal and autophagosomal fusion. The presence of proteins involved in lipid transport may explain the accumulation of lipid bodies in the organelle and the lipid component in neuromelanin structure. The major lipids observed in lipid bodies of the organelle are dolichols with lower amounts of other lipids. Proteins of aggregation and degradation pathways were present, suggesting a role for accumulation by this organelle when the ubiquitin-proteasome system is inadequate. The presence of proteins associated with aging and storage diseases may reflect impaired autophagic degradation or impaired function of lysosomal enzymes. The identification of typical autophagy proteins and double membranes demonstrates the organelle's autophagic nature and indicates that it has engulfed neuromelanin precursors from the cytosol. Based on these data, it appears that the neuromelanin-containing organelle has a very slow turnover during the life of a neuron and represents an intracellular compartment of final destination for numerous molecules not degraded by other systems.

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Tau Does Not Stabilize Axonal Microtubules but Rather Enables Them to Have Long Labile Domains

Liang Qiang[3], Xiaohuan Sun[3], Timothy O. Austin, Hemalatha Muralidharan, Daphney C. Jean, Mei Liu, Wenqian Yu, Peter W. Baas[4]

It is widely believed that tau stabilizes microtubules in the axon [1, 2, 3] and, hence, that disease-induced loss of tau from axonal microtubules leads to their destabilization [3, 4, 5]. An individual microtubule in the axon has a stable domain and a labile domain [6, 7, 8]. We found that tau is more abundant on the labile domain, which is inconsistent with tau's proposed role as a microtubule stabilizer. When tau is experimentally depleted from cultured rat neurons, the labile microtubule mass of the axon drops considerably, the remaining labile microtubule mass becomes less labile, and the stable microtubule mass increases. MAP6 (also called stable tubule-only polypeptide), which is normally enriched on the stable domain [9], acquires a broader distribution across the microtubule when tau is depleted, providing a potential explanation for the increase in stable microtubule mass. When MAP6 is depleted, the labile microtubule mass becomes even more labile, indicating that, unlike tau, MAP6 is a genuine stabilizer of axonal microtubules. We conclude that tau is not a stabilizer of axonal microtubules but is enriched on the labile domain of the microtubule to promote its assembly while limiting the binding to it of genuine stabilizers, such as MAP6. This enables the labile domain to achieve great lengths without being stabilized. These conclusions are contrary to tau dogma.

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Brain. 2018 Jun 26. doi: 10.1093/brain/awy159. [Epub ahead of print]

Trisomy of human chromosome 21 enhances amyloid-β deposition independently of an extra copy of APP.

Wiseman FK[1,2], Pulford LJ[1], Barkus C[3], Liao F[4], Portelius E[5], Webb R[6], Chávez-Gutiérrez L[7], Cleverley K[1], Noy S[1], Sheppard O[1], Collins T[1], Powell C[8], Sarell CJ[8], Rickman M[1], Choong X[1], Tosh JL[1], Siganporia C[1], Whittaker HT[1], Stewart F[4], Szaruga M[7]; London Down syndrome consortium, Murphy MP[6], Blennow K[5], de Strooper B[7,9,10], Zetterberg H[5,9,10], Bannerman D[3], Holtzman DM[4], Tybulewicz VLJ[2,11,12], Fisher EMC[1,2].

⊕ Collaborators (6)

⊕ Author information

Abstract

Down syndrome, caused by trisomy of chromosome 21, is the single most common risk factor for early-onset Alzheimer's disease. Worldwide approximately 6 million people have Down syndrome, and all these individuals will develop the hallmark amyloid plaques and neurofibrillary tangles of Alzheimer's disease by the age of 40 and the vast majority will go on to develop dementia. Triplication of APP, a gene on chromosome 21, is sufficient to cause early-onset Alzheimer's disease in the absence of Down syndrome. However, whether triplication of other chromosome 21 genes influences disease pathogenesis in the context of Down syndrome is unclear. Here we show, in a mouse model, that triplication of chromosome 21 genes other than APP increases amyloid-β aggregation, deposition of amyloid-β plaques and worsens associated cognitive deficits. This indicates that triplication of chromosome 21 genes other than APP is likely to have an important role to play in Alzheimer's disease pathogenesis in individuals who have Down syndrome. We go on to show that the effect of trisomy of chromosome 21 on amyloid-β aggregation correlates with an unexpected shift in soluble amyloid-β 40/42 ratio. This alteration in amyloid-β isoform ratio occurs independently of a change in the carboxypeptidase activity of the γ-secretase complex, which cleaves the peptide from APP, or the rate of extracellular clearance of amyloid-β. These new mechanistic insights into the role of triplication of genes on chromosome 21, other than APP, in the development of Alzheimer's disease in individuals who have Down syndrome may have implications for the treatment of this common cause of neurodegeneration.

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Control of mitochondrial superoxide production by reverse electron transport at complex I

Ellen L. Robb[‡], Andrew R. Hall[‡], Tracy A. Prime[‡], Simon Eaton[§1], Marten Szibor[¶,‖], Carlo Viscomi[‡], Andrew M. James[‡] and Michael P. Murphy[‡2]

The generation of mitochondrial superoxide ($O_2^{\cdot-}$) by reverse electron transport (RET) at complex I causes oxidative damage in pathologies such as ischemia reperfusion injury, but also provides the precursor to H_2O_2 production in physiological mitochondrial redox signaling. Here, we quantified the factors that determine mitochondrial $O_2^{\cdot-}$ production by RET in isolated heart mitochondria. Measuring mitochondrial H_2O_2 production at a range of proton-motive force (Δp) values and for several coenzyme Q (CoQ) and NADH pool redox states obtained with the uncoupler *p*-trifluoromethoxyphenylhydrazone, we show that $O_2^{\cdot-}$ production by RET responds to changes in O_2 concentration, the magnitude of Δp, and the redox states of the CoQ and NADH pools. Moreover, we determined how expressing the alternative oxidase from the tunicate *Ciona intestinalis* to oxidize the CoQ pool affected RET-mediated $O_2^{\cdot-}$ production at complex I, underscoring the importance of the CoQ pool for mitochondrial $O_2^{\cdot-}$ production by RET. An analysis of $O_2^{\cdot-}$ production at complex I as a function of the thermodynamic forces driving RET at complex I revealed that many molecules that affect mitochondrial reactive oxygen species production do so by altering the overall thermodynamic driving forces of RET, rather than by directly acting on complex I. These findings clarify the factors controlling RET-mediated mitochondrial $O_2^{\cdot-}$ production in both pathological and physiological conditions. We conclude that $O_2^{\cdot-}$ production by RET is highly responsive to small changes in Δp and the CoQ redox state, indicating that complex I RET represents a major mode of mitochondrial redox signaling.

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A parthenogenetic quasi-program causes teratoma-like tumors during aging in wild-type *C. elegans*

A long-standing belief is that aging (senescence) is the result of stochastic damage accumulation. Alternatively, senescent pathology may also result from late-life, wild-type gene action (i.e., antagonistic pleiotropy, as argued by Williams) leading to non-adaptive run-on of developmental programs (or *quasi-programs*) (as suggested more recently by Blagosklonny). In this study, we use existing and new data to show how uterine tumors, a prominent form of senescent pathology in the nematode *Caenorhabditis elegans*, likely result from quasi-programs. Such tumors develop from unfertilized oocytes which enter the uterus and become hypertrophic and replete with endoreduplicated chromatin masses. Tumor formation begins with ovulation of unfertilized oocytes immediately after exhaustion of sperm stocks. We show that the timing of this transition between program and quasi-program (i.e., the onset of senescence), and the onset of tumor formation, depends upon the timing of sperm depletion. We identify homology between uterine tumors and mammalian ovarian teratomas, which both develop from oocytes that fail to mature after meiosis I. In teratomas, futile activation of developmental programs leads to the formation of differentiated structures within the tumor. We report that older uterine tumors express markers of later embryogenesis, consistent with teratoma-like activation of developmental programs. We also present evidence of coupling of distal gonad atrophy to oocyte hypertrophy. This study shows how the Williams Blagosklonny model can provide a mechanistic explanation of this component of *C. elegans* aging. It also suggests etiological similarity between teratoma and some forms of senescent pathology, insofar as both are caused by quasi-programs.

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The association of lifetime alcohol use with mortality and cancer risk in older adults: A cohort study

Andrew T. Kunzmann, Helen G. Coleman, Wen-Yi Huang, Sonja I. Berndt

Methods and findings

We report a population-based cohort study using data from 99,654 adults (68.7% female), aged 55–74 years, participating in the U.S. Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. Cox proportional hazards models assessed the risk of overall and cause-specific mortality, cancer incidence (excluding nonmelanoma skin cancer), and combined risk of cancer and death across categories of self-reported average lifetime alcohol intakes, with adjustment for potential confounders. During 836,740 person-years of follow-up (median 8.9 years), 9,599 deaths and 12,763 primary cancers occurred. Positive linear associations were observed between lifetime alcohol consumption and cancer-related mortality and total cancer incidence. J-shaped associations were observed between average lifetime alcohol consumption and overall mortality, cardiovascular-related mortality, and combined risk of death or cancer. In comparison to lifetime light alcohol drinkers (1–3 drinks per week), lifetime never or infrequent drinkers (<1 drink/week), as well as heavy (2–<3 drinks/day) and very heavy drinkers (3+ drinks/day) had increased overall mortality and combined risk of cancer or death. Corresponding hazard ratios (HRs) and 95% confidence intervals (CIs) for combined risk of cancer or death, respectively, were 1.09 (1.01–1.13) for never drinkers, 1.08 (1.03–1.13) for infrequent drinkers, 1.10 (1.02–1.18) for heavy drinkers, and 1.21 (1.13–1.30) for very heavy drinkers. This analysis is limited to older adults, and residual confounding by socioeconomic factors is possible.

Conclusions

The study supports a J-shaped association between alcohol and mortality in older adults, which remains after adjustment for cancer risk. The results indicate that intakes below 1 drink per day were associated with the lowest risk of death.

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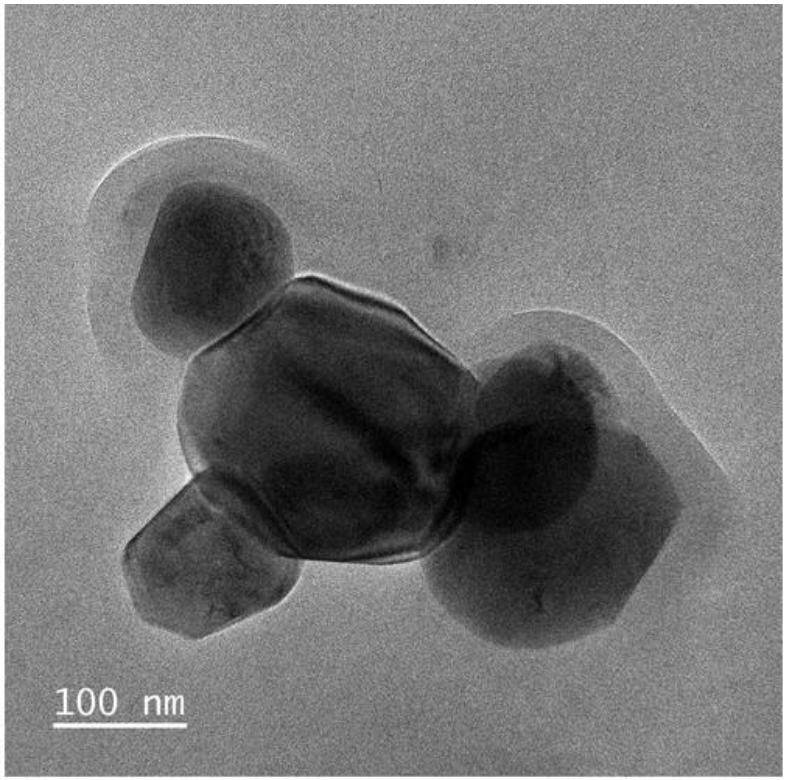
Association of Type 2 Diabetes with Submicron Titanium Dioxide Crystals in the Pancreas

Adam Heller*† , Karalee Jarvis‡ , and Sheryl S. Coffman†



Pigment-grade titanium dioxide (TiO_2) of 200–300 nm particle diameter is the most widely used submicron-sized particle material. Inhaled and ingested TiO_2 particles enter the bloodstream, are phagocytized by macrophages and neutrophils, are inflammatory, and activate the NLRP3 inflammasome. In this pilot study of 11 pancreatic specimens, 8 of the type 2 diabetic pancreas and 3 of the nondiabetic pancreas, we show that particles comprising 110 ± 70 nm average diameter TiO_2 monocrystals abound in the type 2 diabetic pancreas, but not in the nondiabetic pancreas. In the type 2 diabetic pancreas, the count of the crystals is as high as 10^8–10^9 per gram.

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J Proteomics. 2018 Jun 20. pii: S1874-3919(18)30253-7. doi: 10.1016/j.jprot.2018.06.009. [Epub ahead of print]

Proteomic study of endothelial dysfunction induced by AGEs and its possible role in diabetic cardiovascular complications.

Banarjee R[1], Sharma A[2], Bai S[1], Deshmukh A[1], Kulkarni M[3].

⊕ Author information

Abstract

Endothelial dysfunction is one of the primary steps in the development of diabetes associated cardiovascular diseases. Hyperglycemic condition in diabetes promotes accumulation of advanced glycation end products (AGEs) in the plasma, that interact with the receptor for AGEs (RAGE) present on the endothelial cells and negatively affect their function. Using Human umbilical vascular endothelial cells (HUVECs) in culture, the effect of glycated human serum albumin on global proteomic changes was studied by SWATH-MS, a label free quantitative proteomic approach. Out of the 1860 proteins identified, 161 showed higher abundance while 123 showed lesser abundance in cells treated with glycated HSA. Bioinformatic analysis revealed that the differentially regulated proteins were involved in various processes such as apoptosis, oxidative stress etc. that are associated with endothelial dysfunction. Furthermore, the iRegulon analysis and immunofuorescence studies indicated that several of the differentially regulated proteins were transcriptionally regulated by NF-κB, that is downstream to AGE-RAGE axis. Some of the important differentially regulated proteins include ICAM1, vWF, PAI-1that affect important endothelial functions like cell adhesion and blood coagulation. qPCR analysis showed an increase in expression of the AGE receptor RAGE along with other genes involved in endothelial function. AGE treatment to HUVEC cells led to increased oxidative stress and apoptosis. This is the first proteomics study that provides insight into proteomic changes downstream to AGE-RAGE axis leading to endothelial dysfunction and predisposing to cardiovascular complications.

SIGNIFICANCE: Cardiovascular disease (CVD) is a major pathological outcome in diabetic patients and it is important to address ways that target its development before the onset. Elevated plasma AGEs in diabetes can affect endothelial function and can continue to show their effects even after blood glucose levels are back to normal. Since endothelial dysfunction acts as one of the initiating factors for the development of CVD, understanding how AGEs affect the endothelial cell proteome to cause dysfunction will provide insight into the mechanisms involved and aid designing new therapeutic approaches.

J Phys Chem B. 2018 Jun 29. doi: 10.1021/acs.jpcb.8b03983. [Epub ahead of print]

Copper Binding Induces Polymorphism in Amyloid-β Peptide: Results of Computational Models.

Pham DQH, Li MS, La Penna G.

Abstract

Amyloid-β peptides are intrinsically disordered peptides and their aggregation is the hallmark of Alzheimer's Disease (AD) development. The propensity of the amyloid-β (Aβ) peptide to intermolecular interactions, the latter favoring different types of oligomers and aggregated forms, has been the object of a huge number of studies. Several facts are now established: the presence of large amount of d-block (M) ions (Zn, Cu, Fe) in the aggregated forms; the 1:1 M:Aβ ratio favors the formation of amorphous aggregates, with an aggregation rate lower than that in the absence of such ions. In particular, statistical models describing the interactions between copper and amyloid peptides are mandatory to explain the relationship between neurodegeneration, copper dyshomeostasis, and overproduction of reactive oxygen species, the latter event occurring with aging. In this work, we show, by replica-exchange molecular dynamics simulations, that a copper ion (Cu^{2+}) bound as in the experimentally observed prevailing coordination, enhances the probability of closed structures that hinder the formation of extended intermolecular hydrogen bonds that stabilize fibrillar ordered aggregated forms. On the other hand, this effect enhances the catalytic role of the complex during the lifetime of soluble forms.

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A window into extreme longevity; the circulating metabolomic signature of the naked mole-rat, a mammal that shows negligible senescence

Mouse-sized naked mole-rats (*Heterocephalus glaber*), unlike other mammals, do not conform to Gompertzian laws of age-related mortality; adults show no age-related change in mortality risk. Moreover, we observe negligible hallmarks of aging with well-maintained physiological and molecular functions, commonly altered with age in other species. We questioned whether naked mole-rats, living an order of magnitude longer than laboratory mice, exhibit different plasma metabolite profiles, which could then highlight novel mechanisms or targets involved in disease and longevity. Using a comprehensive, unbiased metabolomics screen, we observe striking inter-species differences in amino acid, peptide, and lipid metabolites. Low circulating levels of specific amino acids, particularly those linked to the methionine pathway, resemble those observed during the fasting period at late torpor in hibernating ground squirrels and those seen in longer-lived methionine-restricted rats. These data also concur with metabolome reports on long-lived mutant mice, including the Ames dwarf mice and calorically restricted mice, as well as fruit flies, and even show similarities to circulating metabolite differences observed in young human adults when compared to older humans. During evolution, some of these beneficial nutrient/stress response pathways may have been positively selected in the naked mole-rat. These observations suggest that interventions that modify the aging metabolomic profile to a more youthful one may enable people to lead healthier and longer lives.

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Calorie restriction induces reversible lymphopenia and lymphoid organ atrophy due to cell redistribution

Calorie restriction (CR) without malnutrition increases life span and health span in multiple model organisms. In non-human and human primates, CR causes changes that protect against several age-related pathologies, reduces inflammation, and preserves or improves cell-mediated immunity. However, CR has also been shown to exhibit adverse effects on certain organs and systems, including the immune system, and to impact genetically different organisms of the same species differentially. Alternately, short periods of fasting followed by refeeding may result in the proliferation of bone marrow stem cells, suggesting a potential rejuvenation effect that could impact the hematopoietic compartment. However, the global consequences of CR followed by refeeding on the immune system have not been carefully investigated. Here, we show that individuals practicing long-term CR with adequate nutrition have markedly lower circulating levels of total leukocytes, neutrophils, lymphocytes, and monocytes. In 10-month-old mice, short-term CR lowered lymphocyte cellularity in multiple lymphoid tissues, but not in bone marrow, which appears to be a site of influx, or a "safe haven" for B, NK, and T cells during CR. Cellular loss and redistribution was reversed within the first week of refeeding. Based on BrdU incorporation and Ki67 expression assays, repopulating T cells exhibited high proliferation in the refeeding group following CR. Finally, we demonstrated that the thymus was not essential for T cell repopulation following refeeding. These findings are of potential relevance to strategies to rejuvenate the immune system in mammals and warrant further investigation.

REVIEWS/COMMENTS/ METHODS/EDITORIALS

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Telomerase May Paradoxically Accelerate Aging of the DNA Methylome

Mendelsohn Andrew R. and Larrick James W.

Published Online: 1 Apr 2018 | https://doi.org/10.1089/rej.2018.2073

Abstract

DNA methylation (DNAm) clocks such as the Horvath DNAm clock provide the most accurate biological determination of biological age relative to chronological age available today. However, there is little correlation between DNAm clocks, telomere-based aging clocks, and transcriptomic-based aging clocks. Recently, a genome-wide association study identified single-nucleotide polymorphism variants of TERT, the gene that encodes telomerase, as accelerating intrinsic aging in the Horvath DNAm clock. These same variants have been previously associated with long telomeres in leukocytes, suggesting that TERT acts paradoxically on telomere-associated aging and DNAm-associated aging. In dividing fibroblasts, ectopic expression of TERT accelerated the Horvath intrinsic DNAm clock. However, it is little appreciated that TERT may be expressed at low levels transiently in somatic cells and may play a role in chromatin maintenance and DNA repair. We hypothesize that *TERT may interfere with the maintenance of patterns of DNA methylation in proliferating cells, perhaps by altering regulators of DNA repair and maintenance of chromatin.* The implications of these findings for life span extension and the development of antiaging therapeutics are profound.

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Nuclear Genomic Instability and Aging

Laura J. Niedernhofer,[1] Aditi U. Gurkar,[1,2]
Yinsheng Wang,[3] Jan Vijg,[4] Jan H.J. Hoeijmakers,[5]
and Paul D. Robbins[1]

Loss of protein homeostasis (proteostasis) is a common feature of aging and disease that is characterized by the appearance of nonnative protein aggregates in various tissues. Protein aggregation is routinely suppressed by the proteostasis network (PN), a collection of macromolecular machines that operate in diverse ways to maintain proteome integrity across subcellular compartments and between tissues to ensure a healthy life span. Here, we review the composition, function, and organizational properties of the PN in the context of individual cells and entire organisms and discuss the mechanisms by which disruption of the PN, and related stress response pathways, contributes to the initiation and progression of disease. We explore emerging evidence that disease susceptibility arises from early changes in the composition and activity of the PN and propose that a more complete understanding of the temporal and spatial properties of the PN will enhance our ability to develop effective treatments for protein conformational diseases.

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The effects of donor age on organ transplants: A review and implications for aging research

Jose Carlos Dayoub [a], Franco Cortese [b], Andreja Anžič [a], Tjaša Grum [a], João Pedro de Magalhães [a, b]

Despite the considerable amount of data available on the effect of donor age upon the outcomes of organ transplantation, these still represent an underutilized resource in aging research. In this review, we have compiled relevant studies that analyze the effect of donor age in graft and patient survival following liver, kidney, pancreas, heart, lung and cornea transplantation, with the aim of deriving insights into possible differential aging rates between the different organs. Overall, older donor age is associated with worse outcomes for all the organs studied. Nonetheless, the donor age from which the negative effects upon graft or patient survival starts to be significant varies between organs. In kidney transplantation, this age is within the third decade of life while the data for heart transplantation suggest a significant effect starting from donors over age 40. This threshold was less defined in liver transplantation where it ranges between 30 and 50 years. The results for the pancreas are also suggestive of a detrimental effect starting at a donor age of around 40, although these are mainly derived from simultaneous pancreas-kidney transplantation data. In lung transplantation, a clear effect was only seen for donors over 65, with negative effects of donor age upon transplantation outcomes likely beginning after age 50. Corneal transplants appear to be less affected by donor age as the majority of studies were unable to find any effect of donor age during the first few years posttransplantation. Overall, patterns of the effect of donor age in patient and graft survival were observed for several organ types and placed in the context of knowledge on aging.

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Nat Rev Cancer. 2018 Jul;18(7):433-441. doi: 10.1038/s41568-018-0004-9.

Mechanisms of cancer resistance in long-lived mammals.

Seluanov A[1], Gladyshev VN[2], Vijg J[3], Gorbunova V[4].

⊕ Author information

Abstract

Cancer researchers have traditionally used the mouse and the rat as staple model organisms. These animals are very short-lived, reproduce rapidly and are highly prone to cancer. They have been very useful for modelling some human cancer types and testing experimental treatments; however, these cancer-prone species offer little for understanding the mechanisms of cancer resistance. Recent technological advances have expanded bestiary research to non-standard model organisms that possess unique traits of very high value to humans, such as cancer resistance and longevity. In recent years, several discoveries have been made in non-standard mammalian species, providing new insights on the natural mechanisms of cancer resistance. These include mechanisms of cancer resistance in the naked mole rat, blind mole rat and elephant. In each of these species, evolution took a different path, leading to novel mechanisms. Many other long-lived mammalian species display cancer resistance, including whales, grey squirrels, microbats, cows and horses. Understanding the molecular mechanisms of cancer resistance in all these species is important and timely, as, ultimately, these mechanisms could be harnessed for the development of human cancer therapies.

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Am J Physiol Heart Circ Physiol. 2018 Jun 27. doi: 10.1152/ajpheart.00100.2018. [Epub ahead of print]

Emerging Roles of Extracellular Vesicles in Cardiac Repair and Rejuvenation.

Alibhai FJ[1], Tobin SW[2], Yeganeh A[2], Weisel RD[3], Li RK[4].

Author information

Abstract

Cell therapy has received significant attention as a therapeutic approach to restore cardiac function after myocardial infarction. Accumulating evidence supports that beneficial effects observed with cell therapy are due to paracrine secretion of multiple factors from transplanted cells which alter the tissue microenvironment and orchestrate cardiac repair processes. Of these paracrine factors, extracellular vesicles (EVs) have emerged as a key effector of cell therapy. EVs regulate cellular function through the transfer of cargo such as microRNAs and proteins which act on multiple biological pathways within recipient cells. These discoveries have led to the development of cell-free therapies using EVs to improve cardiac repair after a myocardial infarction. Here, we present an overview of the current use of EVs to enhance cardiac repair following myocardial infarction. We also discuss the emerging use of EVs for rejuvenation-based therapies. Lastly, future directions for the use of EVs as therapeutic agents for cardiac regenerative medicine will also be discussed.

Extracellular vesicles characteristics and emerging roles in atherosclerotic cardiovascular disease

Anouar Hafiane, Stella S. Daskalopoulou

The term extracellular vesicles (EVs) describes membrane vesicles released into the extracellular space by most cell types. EVs have been recognized to play an important role in cell-to-cell communication. They are known to contain various bioactive molecules, including proteins, lipids, and nucleic acids. Although the nomenclature of EVs is not entirely standardized, they are considered to include exosomes, microparticles or microvesicles and apoptotic bodies. EVs are believed to play important roles in a wide range of biological processes. Although the pathogenic roles of EVs are largely documented, their protective roles are not as well established. Cardiovascular disease represents one of the most relevant and rapidly growing areas of the EV research. Circulating EVs released from platelets, erythrocytes, leukocytes, and endothelial cells may contain potentially valuable biological information for biomarker development in cardiovascular disease and could serve as a vehicle for therapeutic use. Herein, we provide an overview of the current knowledge in EV in cardiovascular disease, including a discussion on challenges in EV research, EV properties in various cell types, and their importance in atherosclerotic disease.

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Biol Chem. 2018 Apr 25;399(5):421-436. doi: 10.1515/hsz-2017-0331.

Update on mitochondria and muscle aging: all wrong roads lead to sarcopenia.

Picca A[1], Calvani R[1], Bossola M[2], Allocca E[1], Menghi A[1], Pesce V[3], Lezza AMS[3], Bernabei R[1], Landi F[1], Marzetti E[1].

Author information

Abstract

Sarcopenia is a well-known geriatric syndrome that has been endorsed over the years as a biomarker allowing for the discrimination, at a clinical level, of biological from chronological age. Multiple candidate mechanisms have been linked to muscle degeneration during sarcopenia. Among them, there is wide consensus on the central role played by the loss of mitochondrial integrity in myocytes, secondary to dysfunctional quality control mechanisms. Indeed, mitochondria establish direct or indirect contacts with other cellular components (e.g. endoplasmic reticulum, peroxisomes, lysosomes/vacuoles) as well as the extracellular environment through the release of several biomolecules. The functional implications of these interactions in the context of muscle physiology and sarcopenia are not yet fully appreciated and represent a promising area of investigation. Here, we present an overview of recent findings concerning the interrelation between mitochondrial quality control processes, inflammation and the metabolic regulation of muscle mass in the pathogenesis of sarcopenia highlighting those pathways that may be exploited for developing preventive and therapeutic interventions against muscle aging.

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Progress in Molecular Biology and Translational Science

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Metabolic Aspects of Aging

Edited by MARY ANN OTTINGER

Volume 155, Pages 1-136 (2018)

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Induction and Validation of Cellular Senescence in Primary Human Cells

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Cellular senescence is a state of permanent cell cycle arrest activated in response to different damaging stimuli. Activation of cellular senescence is a hallmark of various pathophysiological conditions including tumor suppression, tissue remodeling and aging. The inducers of cellular senescence *in vivo* are still poorly characterized. However, a number of stimuli can be used to promote cellular senescence *ex vivo*. Among them, most common senescence-inducers are replicative exhaustion, ionizing and non-ionizing radiation, genotoxic drugs, oxidative stress, and demethylating and acetylating agents. Here, we will provide detailed instructions on how to use these stimuli to induce fibroblasts into senescence. This protocol can easily be adapted for different types of primary cells and cell lines, including cancer cells. We also describe different methods for the validation of senescence induction. In particular, we focus on measuring the activity of the lysosomal enzyme Senescence-Associated β-galactosidase (SA-β-gal), the rate of DNA synthesis using 5-ethynyl-2'-deoxyuridine (EdU) incorporation assay, the levels of expression of the cell cycle inhibitors p16 and p21, and the expression and secretion of members of the Senescence-Associated Secretory Phenotype (SASP). Finally, we provide example results and discuss further applications of these protocols.

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Biochemistry. 2018 May 29;57(21):3036-3049. doi: 10.1021/acs.biochem.8b00170. Epub 2018 May 15.

RPtag as an Orally Bioavailable, Hyperstable Epitope Tag and Generalizable Protein Binding Scaffold.

DeRosa JR[1,2], Moyer BS[1,2], Lumen E[1,2], Wolfe AJ[1,2], Sleeper MB[1,2], Bianchi AH[1,2], Crawford A[1,2], McGuigan C[1,2], Wortel D[1,2], Fisher C[1,2], Moody KJ[1,2], Blanden AR[1,2].

⊕ Author information

Abstract

Antibodies are the most prolific biologics in research and clinical environments because of their ability to bind targets with high affinity and specificity. However, antibodies also carry liabilities. A significant portion of the life-science reproducibility crisis is driven by inconsistent performance of research-grade antibodies, and clinical antibodies are often unstable and require costly cold-chain management to reach their destinations in active form. In biotechnology, antibodies are also limited by difficulty integrating them in many recombinant systems due to their size and structural complexity. A switch to small, stable, sequence-verified binding scaffolds may overcome these barriers. Here we present such a scaffold, RPtag, based on a ribose-binding protein (RBP) from extremophile Caldanaerobacter subterraneus. RPtag binds an optimized peptide with pM affinity, is stable to extreme temperature, pH, and protease treatment, readily refolds after denaturation, is effective in common laboratory applications, was rationally engineered to bind bioactive PDGF-β, and was formulated as a gut-stable orally bioavailable preparation.

Int J Biol Macromol. 2018 Jun 24. pii: S0141-8130(18)30483-5. doi: 10.1016/j.ijbiomac.2018.06.102. [Epub ahead of print]

An in-silico method for identifying aggregation rate enhancer and mitigator mutations in proteins.

Rawat P[1], Kumar S[2], Michael Gromiha M[3].

Author information

Abstract

Newly synthesized polypeptides must pass stringent quality controls in cells to ensure appropriate folding and function. However, mutations, environmental stresses and aging can reduce efficiencies of these controls, leading to accumulation of protein aggregates, amyloid fibrils and plaques. In-vitro experiments have shown that even single amino acid substitutions can drastically enhance or mitigate protein aggregation kinetics. In this work, we have collected a dataset of 220 unique mutations in 25 proteins and classified them as enhancers or mitigators on the basis of their effect on protein aggregation rate. The data were analyzed via machine learning to identify features capable of distinguishing between aggregation rate enhancers and mitigators. Our initial Support Vector Machine (SVM) model separated such mutations with an overall accuracy of 69%. When local secondary structures at the mutation sites were considered, the accuracies further improved by 13-15%. The machine-learnt features are distinct for each secondary structure class at mutation sites. Protein stability and flexibility changes are important features for mutations in α-helices. β-strand propensity, polarity and charge become important when mutations occur in β-strands and ability to form secondary structure, helical tendency and aggregation propensity are important for mutations lying in coils. These results have been incorporated into a sequence-based algorithm (available at http://www.iitm.ac.in/bioinfo/aggrerate-disc/) capable of predicting whether a mutation will enhance or mitigate a protein's aggregation rate. This algorithm will find several applications towards understanding protein aggregation in human diseases, enable in-silico optimization of biopharmaceuticals and enzymes for improved biophysical attributes and de novo design of bio-nanomaterials.

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Measurement of respiratory function in isolated cardiac mitochondria using Seahorse XFe24 Analyzer: applications for aging research

Authors | Authors and affiliations

Siva S. V. P. Sakamuri, Jared A. Sperling, Venkata N. Sure, Monica H. Dholakia, Nicholas R. Peterson, Ibolya Rutkai, Padmini S. Mahalingam, Ryosuke Satou, Prasad V. G. Katakam

Mitochondria play a critical role in the cardiomyocyte physiology by generating majority of the ATP required for the contraction/relaxation through oxidative phosphorylation (OXPHOS). Aging is a major risk factor for cardiovascular diseases (CVD) and mitochondrial dysfunction has been proposed as potential cause of aging. Recent technological innovations in Seahorse XFe24 Analyzer enhanced the detection sensitivity of oxygen consumption rate and proton flux to advance our ability study mitochondrial function. Studies of the respiratory function tests in the isolated mitochondria have the advantages to detect specific defects in the mitochondrial protein function and evaluate the direct mitochondrial effects of therapeutic/pharmacological agents. Here, we provide the protocols for studying the respiratory function of isolated murine cardiac mitochondria by measuring oxygen consumption rate using Seahorse XFe24 Analyzer. In addition, we provide details about experimental design, measurement of various respiratory parameters along with interpretation and analysis of data.

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CRISPR base editors: genome editing without double-stranded breaks

Ayman Eid, Sahar Alshareef, Magdy M. Mahfouz

Biochemical Journal

The CRISPR (clustered regularly interspaced short palindromic repeat)/Cas9 adaptive immunity system has been harnessed for genome editing applications across eukaryotic species, but major drawbacks, such as the inefficiency of precise base editing and off-target activities, remain. A catalytically inactive Cas9 variant (dead Cas9, dCas9) has been fused to diverse functional domains for targeting genetic and epigenetic modifications, including base editing, to specific DNA sequences. As base editing does not require the generation of double-strand breaks, dCas9 and Cas9 nickase have been used to target deaminase domains to edit specific loci. Adenine and cytidine deaminases convert their respective nucleotides into other DNA bases, thereby offering many possibilities for DNA editing. Such base-editing enzymes hold great promise for applications in basic biology, trait development in crops, and treatment of genetic diseases. Here, we discuss recent advances in precise gene editing using different platforms as well as their potential applications in basic biology and biotechnology.

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J Cell Biol. 2018 Jun 25. pii: jcb.201711048. doi: 10.1083/jcb.201711048. [Epub ahead of print]

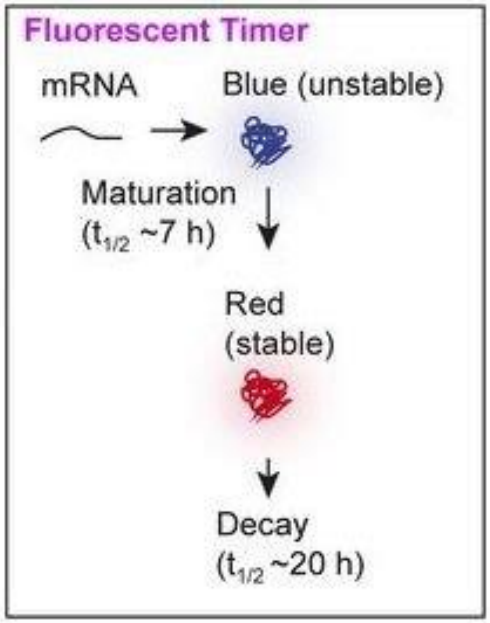
A timer for analyzing temporally dynamic changes in transcription during differentiation in vivo.

Bending D[1], Martín PP[1], Paduraru A[1], Ducker C[1], Marzaganov E[1], Laviron M[1], Kitano S[2], Miyachi H[2], Crompton T[3], Ono M[4].

Author information

Abstract

Understanding the mechanisms of cellular differentiation is challenging because differentiation is initiated by signaling pathways that drive temporally dynamic processes, which are difficult to analyze in vivo. We establish a new tool, Timer of cell kinetics and activity (Tocky; or toki [time in Japanese]). Tocky uses the fluorescent Timer protein, which spontaneously shifts its emission spectrum from blue to red, in combination with computer algorithms to reveal the dynamics of differentiation in vivo. Using a transcriptional target of T cell receptor (TCR) signaling, we establish *Nr4a3*-Tocky to follow downstream effects of TCR signaling. *Nr4a3*-Tocky reveals the temporal sequence of events during regulatory T cell (Treg) differentiation and shows that persistent TCR signals occur during Treg generation. Remarkably, antigen-specific T cells at the site of autoimmune inflammation also show persistent TCR signaling. In addition, by generating Foxp3-Tocky, we reveal the in vivo dynamics of demethylation of the *Foxp3* gene. Thus, Tocky is a tool for cell biologists to address previously inaccessible questions by directly revealing dynamic processes in vivo.



OTHER RESEARCH

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2017 in review: FDA approvals of new molecular entities

Michael S. Kinch, michael.kinch@wustl.edu **and Rebekah H. Griesenauer**

An overview of drugs approved by the FDA in 2017 reflected a reversion to the mean after a low number of NME approvals in 2016. This reversal was largely driven by the largest number of biologics-based NMEs recorded to date, which offset an average number of small-molecule approvals. Oncology indications continued to dominate followed by novel treatments for infectious, immunologic and neurologic diseases. From a mechanistic standpoint, the industry has continued a trend of target diversification, reflecting advances in scientific understanding of disease processes. Finally, 2017 continued a period of relatively few mergers and acquisitions, which broke a more-than-a-decade-long decline in the number of organizations contributing to research and development.

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Reversal of siRNA-mediated gene silencing *in vivo*

Ivan Zlatev, Adam Castoreno, Christopher R Brown, June Qin, Scott Waldron, Mark K Schlegel, Rohan Degaonkar, Svetlana Shulga-Morskaya, Huilei Xu, Swati Gupta, Shigeo Matsuda, Akin Akinc, Kallanthottathil G Rajeev, Muthiah Manoharan, Martin A Maier & Vasant Jadhav

We report rapid, potent reversal of GalNAc-siRNA-mediated RNA interference (RNAi) activity *in vivo* with short, synthetic, high-affinity oligonucleotides complementary to the siRNA guide strand. We found that 9-mers with five locked nucleic acids (LNAs) have the highest potency across several targets. Our modular, sequence-specific approach, named REVERSIR, may enhance the therapeutic profile of any long-acting GalNAc–siRNA (short interfering RNA) conjugate by enabling control of RNAi pharmacology.

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Adenine base editing in mouse embryos and an adult mouse model of Duchenne muscular dystrophy

Seuk-Min Ryu[1,2,4], Taeyoung Koo[1,4], Kyoungmi Kim[1,3,4], Kayeong Lim[1,2,4], Gayoung Baek[1], Sang-Tae Kim[1], Heon Seok Kim[1,2], Da-eun Kim[1,2], Hyunji Lee[1], Eugene Chung[1,2] & Jin-Soo Kim[1,2]

Adenine base editors (ABEs) composed of an engineered adenine deaminase and the *Streptococcus pyogenes* Cas9 nickase enable adenine-to-guanine (A-to-G) single-nucleotide substitutions in a guide RNA (gRNA)-dependent manner. Here we demonstrate application of this technology in mouse embryos and adult mice. We also show that long gRNAs enable adenine editing at positions one or two bases upstream of the window that is accessible with standard single guide RNAs (sgRNAs). We introduced the Himalayan point mutation in the *Tyr* gene by microinjecting ABE mRNA and an extended gRNA into mouse embryos, obtaining *Tyr* mutant mice with an albino phenotype. Furthermore, we delivered the split ABE gene, using trans-splicing adeno-associated viral vectors, to muscle cells in a mouse model of Duchenne muscular dystrophy to correct a nonsense mutation in the *Dmd* gene, demonstrating the therapeutic potential of base editing in adult animals.

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Autologous iPSC-Based Vaccines Elicit Anti-tumor Responses *In Vivo*

Cancer cells and embryonic tissues share a number of cellular and molecular properties, suggesting that induced pluripotent stem cells (iPSCs) may be harnessed to elicit anti-tumor responses in cancer vaccines. RNA sequencing revealed that human and murine iPSCs express tumor-associated antigens, and we show here a proof of principle for using irradiated iPSCs in autologous anti-tumor vaccines. In a prophylactic setting, iPSC vaccines prevent tumor growth in syngeneic murine breast cancer, mesothelioma, and melanoma models. As an adjuvant, the iPSC vaccine inhibited melanoma recurrence at the resection site and reduced metastatic tumor load, which was associated with fewer Th17 cells and increased $CD11b^{+}GR1^{hi}$ myeloid cells. Adoptive transfer of T cells isolated from vaccine-treated tumor-bearing mice inhibited tumor growth in unvaccinated recipients, indicating that the iPSC vaccine promotes an antigen-specific anti-tumor T cell response. Our data suggest an easy, generalizable strategy for multiple types of cancer that could prove highly valuable in clinical immunotherapy.

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Deep Phenotyping on Electronic Health Records Facilitates Genetic Diagnosis by Clinical Exomes

Jung Hoon Son[9], Gangcai Xie[9], Chi Yuan, Lyudmila Ena, Ziran Li, Andrew Goldstein, Lulin Huang, Liwei Wang, Feichen Shen, Hongfang Liu, Karla Mehl, Emily E. Groopman, Maddalena Marasa, Krzysztof Kiryluk, Ali G. Gharavi, Wendy K. Chung, George Hripcsak, Carol Friedman, Chunhua Weng[10], Kai Wang[10]

[9] These authors contributed equally to this work

[10] These authors contributed equally to this work

Publication stage: In Press Corrected Proof

PlumX Metrics

DOI: https://doi.org/10.1016/j.ajhg.2018.05.010

Article Info

Summary | Full Text | Methods | Images/Data | References | Related Articles

Integration of detailed phenotype information with genetic data is well established to facilitate accurate diagnosis of hereditary disorders. As a rich source of phenotype information, electronic health records (EHRs) promise to empower diagnostic variant interpretation. However, how to accurately and efficiently extract phenotypes from heterogeneous EHR narratives remains a challenge. Here, we present EHR-Phenolyzer, a high-throughput EHR framework for extracting and analyzing phenotypes. EHR-Phenolyzer extracts and normalizes Human Phenotype Ontology (HPO) concepts from EHR narratives and then prioritizes genes with causal variants on the basis of the HPO-coded phenotype manifestations. We assessed EHR-Phenolyzer on 28 pediatric individuals with confirmed diagnoses of monogenic diseases and found that the genes with causal variants were ranked among the top 100 genes selected by EHR-Phenolyzer for 16/28 individuals ($p < 2.2 \times 10^{-16}$), supporting the value of phenotype-driven gene prioritization in diagnostic sequence interpretation. To assess the generalizability, we replicated this finding on an independent EHR dataset of ten individuals with a positive diagnosis from a different institution. We then assessed the broader utility by examining two additional EHR datasets, including 31 individuals who were suspected of having a Mendelian disease and underwent different types of genetic testing and 20 individuals with positive diagnoses of specific Mendelian etiologies of chronic kidney disease from exome sequencing. Finally, through several retrospective case studies, we demonstrated how combined analyses of genotype data and deep phenotype data from EHRs can expedite genetic diagnoses. In summary, EHR-Phenolyzer leverages EHR narratives to automate phenotype-driven analysis of clinical exomes or genomes, facilitating the broader implementation of genomic medicine.