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Sven Bulterijs

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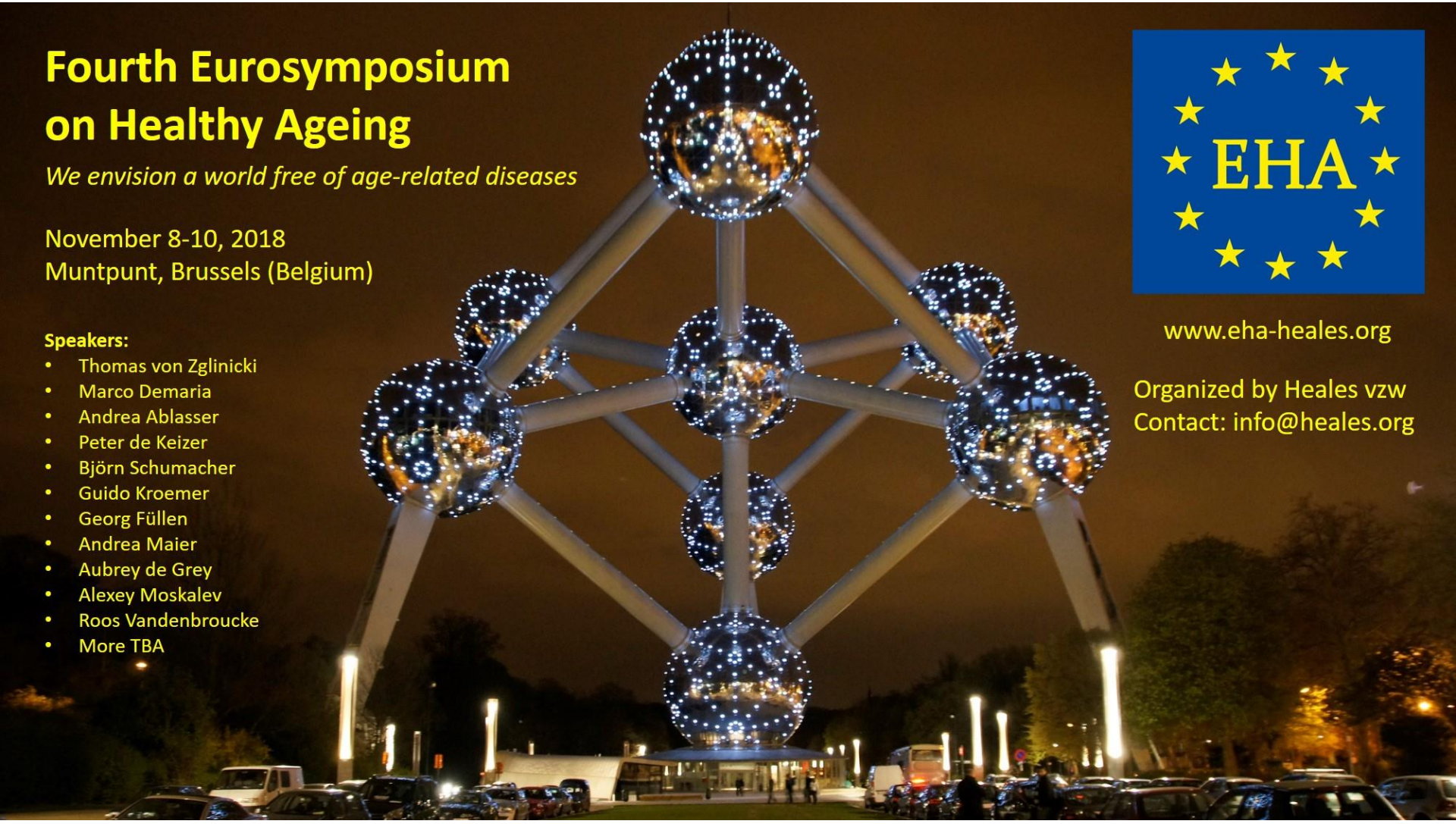
Fourth Eurosymposium on Healthy Ageing

We envision a world free of age-related diseases

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

Speakers:

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



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A randomized control trial to establish the feasibility and safety of rapamycin treatment in an older human cohort: Immunological, physical performance, and cognitive effects

been demonstrated. Towards this end, we undertook a placebo-controlled pilot study in 25 generally healthy older adults (aged 70–95 years); subjects were randomized to receive either 1 mg RAPA or placebo daily. Although three subjects withdrew, 11 RAPA and 14 controls completed at least 8 weeks of treatment and were included in the analysis. We monitored for changes that would indicate detrimental effects of RAPA treatment on metabolism, including both standard clinical laboratory assays (CBC, CMP, HbA1c) and oral glucose tolerance tests (OGTTs). We also monitored parameters typically associated with aging that could potentially be modified by RAPA; these included cognitive function which was assessed by three different tools: Executive Interview-25 (EXIT25); Saint Louis University Mental Status Exam (SLUMS); and Texas Assessment of Processing Speed (TAPS). In addition, physical performance was measured by handgrip strength and 40-foot timed walks. Lastly, changes in general parameters of healthy immune aging, including serum pro-inflammatory cytokine levels and blood cell subsets, were assessed. Five subjects reported potential adverse side effects; in the RAPA group, these were limited to facial rash (1 subject), stomatitis (1 subject) and gastrointestinal issues (2 subjects) whereas placebo treated subjects only reported stomatitis (1 subject). Although no other adverse events were reported, statistically significant decrements in several erythrocyte parameters including hemoglobin (HgB) and hematocrit (Hct) as well as in red blood cell count (RBC), red blood cell distribution width (RDW), mean corpuscular volume (MCV), and mean corpuscular hemoglobin (MCH) were observed in the RAPA-treatment group. None of these changes manifested clinically significant effects during the short duration of this study. Similarly, no changes were noted in any other clinical laboratory, cognitive, physical performance, or self-perceived health status measure over the study period. Immune parameters were largely unchanged as well, possibly due to the advanced ages of the cohort (70–93 years; mean age 80.5). RAPA-associated increases in a myeloid cell subset and in T_{REGS} were detected, but changes in most other PBMC cell subsets were not statistically significant. Importantly, the OGTTs revealed no RAPA-induced change in blood glucose concentration, insulin secretion, and insulin sensitivity. Thus, based on the results of our pilot study, it appears that short-term RAPA treatment can be used safely in older persons who are otherwise healthy; a trial with a larger sample size and longer treatment duration is warranted.

Coupling of *Rigor Mortis* and Intestinal Necrosis during *C. elegans* Organismal Death

Evgeniy R. Galimov, Rosina E. Pryor, Sarah E. Poole, Alexandre Benedetto, Zachary Pincus, David Gems[4]

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Article Info

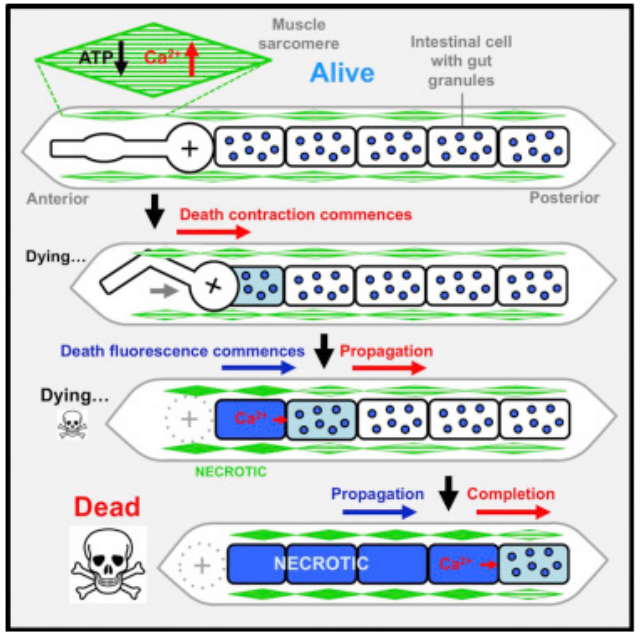
Highlights

- A wave of body wall muscle contraction occurs during *C. elegans* organismal death
- This *rigor mortis*-like phenomenon is coupled to a wave of intestinal necrosis
- Both waves are accompanied by Ca^{2+} release and a drop in ATP levels
- Properties of long-lived *daf-2* mutants suggest resistance to organismal death

Summary

Organismal death is a process of systemic collapse whose mechanisms are less well understood than those of cell death. We previously reported that death in *C. elegans* is accompanied by a calcium-propagated wave of intestinal necrosis, marked by a wave of blue autofluorescence (death fluorescence). Here, we describe another feature of organismal death, a wave of body wall muscle contraction, or death contraction (DC). This phenomenon is accompanied by a wave of intramuscular Ca^{2+} release and, subsequently, of intestinal necrosis. Correlation of directions of the DC and intestinal necrosis waves implies coupling of these death processes. Long-lived insulin/IGF-1-signaling mutants show reduced DC and delayed intestinal necrosis, suggesting possible resistance to organismal death. DC resembles mammalian *rigor mortis*, a postmortem necrosis-related process in which Ca^{2+} influx promotes muscle hyper-contraction. In contrast to mammals, DC is an early rather than a late event in *C. elegans* organismal death.

Graphical Abstract | Video Abstract



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Activation of DAF-16/FOXO by reactive oxygen species contributes to longevity in long-lived mitochondrial mutants in Caenorhabditis elegans.

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Author information

Abstract

Mild deficits in mitochondrial function have been shown to increase lifespan in multiple species including worms, flies and mice. Here, we study three C. elegans mitochondrial mutants (clk-1, isp-1 and nuo-6) to identify overlapping genetic pathways that contribute to their longevity. We find that genes regulated by the FOXO transcription factor DAF-16 are upregulated in all three strains, and that the transcriptional changes present in these worms overlap significantly with the long-lived insulin-IGF1 signaling pathway mutant daf-2. We show that DAF-16 and multiple DAF-16 interacting proteins (MATH-33, IMB-2, CST-1/2, BAR-1) are required for the full longevity of all three mitochondrial mutants. Our results suggest that the activation of DAF-16 in these mutants results from elevated levels of reactive oxygen species. Overall, this work reveals an overlapping genetic pathway required for longevity in three mitochondrial mutants, and, combined with previous work, demonstrates that DAF-16 is a downstream mediator of lifespan extension in multiple pathways of longevity.

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Nicotinamide Improves Aspects of Healthspan, but Not Lifespan, in Mice

Highlights

- Nicotinamide (NAM) supplementation does not extend lifespan in mice
- NAM prevents hepatosteatosis in obese mice while improving glucose metabolism
- NAM reduces oxidative stress and inflammation
- NAM depresses NAM salvage and does not produce a net boost in tissue NAD levels

Summary

The role in longevity and healthspan of nicotinamide (NAM), the physiological precursor of NAD^+, is elusive. Here, we report that chronic NAM supplementation improves healthspan measures in mice without extending lifespan. Untargeted metabolite profiling of the liver and metabolic flux analysis of liver-derived cells revealed NAM-mediated improvement in glucose homeostasis in mice on a high-fat diet (HFD) that was associated with reduced hepatic steatosis and inflammation concomitant with increased glycogen deposition and flux through the pentose phosphate and glycolytic pathways. Targeted NAD metabolome analysis in liver revealed depressed expression of NAM salvage in NAM-treated mice, an effect counteracted by higher expression of *de novo* NAD biosynthetic enzymes. Although neither hepatic NAD^+ nor $NADP^+$ was boosted by NAM, acetylation of some SIRT1 targets was enhanced by NAM supplementation in a diet- and NAM dose-dependent manner. Collectively, our results show health improvement in NAM-supplemented HFD-fed mice in the absence of survival effects.

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NAD^+ supplementation normalizes key Alzheimer's features and DNA damage responses in a new AD mouse model with introduced DNA repair deficiency

Emerging findings suggest that compromised cellular bioenergetics and DNA repair contribute to the pathogenesis of Alzheimer's disease (AD), but their role in disease-defining pathology is unclear. We developed a DNA repair-deficient 3xTgAD/Polβ$^{+/-}$ mouse that exacerbates major features of human AD including phosphorylated Tau (pTau) pathologies, synaptic dysfunction, neuronal death, and cognitive impairment. Here we report that 3xTgAD/Polβ$^{+/-}$ mice have a reduced cerebral NAD^+/NADH ratio indicating impaired cerebral energy metabolism, which is normalized by nicotinamide riboside (NR) treatment. NR lessened pTau pathology in both 3xTgAD and 3xTgAD/Polβ$^{+/-}$ mice but had no impact on amyloid β peptide (Aβ) accumulation. NR-treated 3xTgAD/Polβ$^{+/-}$ mice exhibited reduced DNA damage, neuroinflammation, and apoptosis of hippocampal neurons and increased activity of SIRT3 in the brain. NR improved cognitive function in multiple behavioral tests and restored hippocampal synaptic plasticity in 3xTgAD mice and 3xTgAD/Polβ$^{+/-}$ mice. In general, the deficits between genotypes and the benefits of NR were greater in 3xTgAD/Polβ$^{+/-}$ mice than in 3xTgAD mice. Our findings suggest a pivotal role for cellular NAD^+ depletion upstream of neuroinflammation, pTau, DNA damage, synaptic dysfunction, and neuronal degeneration in AD. Interventions that bolster neuronal NAD^+ levels therefore have therapeutic potential for AD.

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Defective cholesterol clearance limits remyelination in the aged central nervous system

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Abstract

Age-associated decline in regeneration capacity limits the restoration of nervous system functionality after injury. In a model for demyelination, we found that old mice fail to resolve the inflammatory response initiated after myelin damage. Aged phagocytes accumulated excessive amounts of myelin debris, which triggered cholesterol crystal formation and phagolysosomal membrane rupture and stimulated inflammasomes. Myelin debris clearance required cholesterol transporters, including apolipoprotein E. Stimulation of reverse cholesterol transport was sufficient to restore the capacity of old mice to remyelinate lesioned tissue. Thus, cholesterol-rich myelin debris can overwhelm the efflux capacity of phagocytes, resulting in a phase transition of cholesterol into crystals and thereby inducing a maladaptive immune response that impedes tissue regeneration.

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Identification of a highly neurotoxic α-synuclein species inducing mitochondrial damage and mitophagy in Parkinson's disease

Diego Grassi, Shannon Howard, Minghai Zhou, Natalia Diaz-Perez, Nicolai T. Urban, Debbie Guerrero-Given, Naomi Kamasawa, Laura A. Volpicelli-Daley, Philip LoGrasso and Corinne Ida Lasmézas

Exposure of cultured primary neurons to preformed α-synuclein fibrils (PFFs) leads to the recruitment of endogenous α-synuclein and its templated conversion into fibrillar phosphorylated α-synuclein (pα-synF) aggregates resembling those involved in Parkinson's disease (PD) pathogenesis. Pα-synF was described previously as inclusions morphologically similar to Lewy bodies and Lewy neurites in PD patients. We discovered the existence of a conformationally distinct, nonfibrillar, phosphorylated α-syn species that we named "pα-syn*." We uniquely describe the existence of pα-syn* in PFF-seeded primary neurons, mice brains, and PD patients' brains. Through immunofluorescence and pharmacological manipulation we showed that pα-syn* results from incomplete autophagic degradation of pα-synF. Pα-synF was decorated with autophagic markers, but pα-syn* was not. Western blots revealed that pα-syn* was N- and C-terminally trimmed, resulting in a 12.5-kDa fragment and a SDS-resistant dimer. After lysosomal release, pα-syn* aggregates associated with mitochondria, inducing mitochondrial membrane depolarization, cytochrome C release, and mitochondrial fragmentation visualized by confocal and stimulated emission depletion nanoscopy. Pα-syn* recruited phosphorylated acetyl-CoA carboxylase 1 (ACC1) with which it remarkably colocalized. ACC1 phosphorylation indicates low ATP levels, AMPK activation, and oxidative stress and induces mitochondrial fragmentation via reduced lipoylation. Pα-syn* also colocalized with BiP, a master regulator of the unfolded protein response and a resident protein of mitochondria-associated endoplasmic reticulum membranes that are sites of mitochondrial fission and mitophagy. Pα-syn* aggregates were found in Parkin-positive mitophagic vacuoles and imaged by electron microscopy. Collectively, we showed that pα-syn* induces mitochondrial toxicity and fission, energetic stress, and mitophagy, implicating pα-syn* as a key neurotoxic α-syn species and a therapeutic target.

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BACE1 deletion in the adult mouse reverses preformed amyloid deposition and improves cognitive functions

Xiangyou Hu, Brati Das, Hailong Hou, Wanxia He, Riqiang Yan

BACE1 initiates the generation of the β-amyloid peptide, which likely causes Alzheimer's disease (AD) when accumulated abnormally. BACE1 inhibitory drugs are currently being developed to treat AD patients. To mimic BACE1 inhibition in adults, we generated BACE1 conditional knockout ($BACE1^{fl/fl}$) mice and bred $BACE1^{fl/fl}$ mice with ubiquitin-Cre^{ER} mice to induce deletion of BACE1 after passing early developmental stages. Strikingly, sequential and increased deletion of BACE1 in an adult AD mouse model (5xFAD) was capable of completely reversing amyloid deposition. This reversal in amyloid deposition also resulted in significant improvement in gliosis and neuritic dystrophy. Moreover, synaptic functions, as determined by long-term potentiation and contextual fear conditioning experiments, were significantly improved, correlating with the reversal of amyloid plaques. Our results demonstrate that sustained and increasing BACE1 inhibition in adults can reverse amyloid deposition in an AD mouse model, and this observation will help to provide guidance for the proper use of BACE1 inhibitors in human patients.

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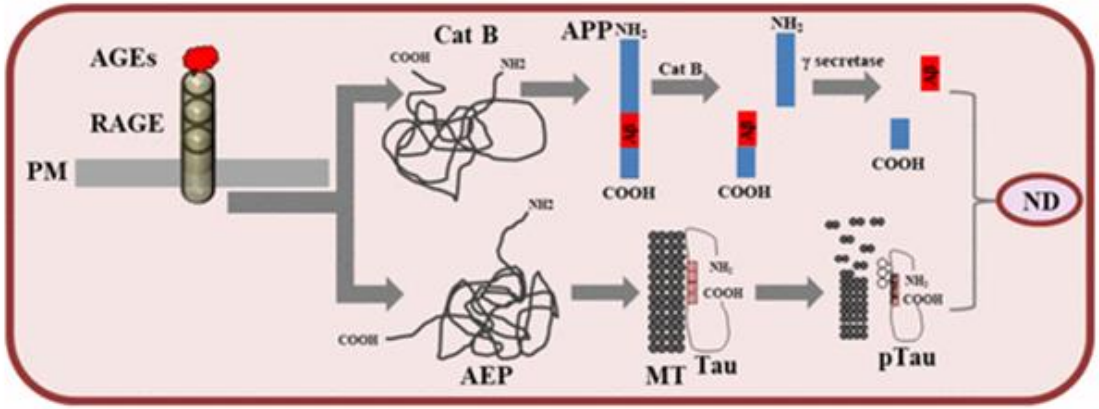
Dysregulation of the epigenetic landscape of normal aging in Alzheimer's disease

Raffaella Nativio, Greg Donahue, Amit Berson, Yemin Lan, Alexander Amlie-Wolf, Ferit Tuzer, Jon B. Toledo, Sager J. Gosai, Brian D. Gregory, Claudio Torres, John Q. Trojanowski, Li-San Wang, F. Brad Johnson ✉, Nancy M. Bonini ✉ & Shelley L. Berger ✉

Aging is the strongest risk factor for Alzheimer's disease (AD), although the underlying mechanisms remain unclear. The chromatin state, in particular through the mark H4K16ac, has been implicated in aging and thus may play a pivotal role in age-associated neurodegeneration. Here we compare the genome-wide enrichment of H4K16ac in the lateral temporal lobe of AD individuals against both younger and elderly cognitively normal controls. We found that while normal aging leads to H4K16ac enrichment, AD entails dramatic losses of H4K16ac in the proximity of genes linked to aging and AD. Our analysis highlights the presence of three classes of AD-related changes with distinctive functional roles. Furthermore, we discovered an association between the genomic locations of significant H4K16ac changes with genetic variants identified in prior AD genome-wide association studies and with expression quantitative trait loci. Our results establish the basis for an epigenetic link between aging and AD.

Advanced Glycation End Products Modulate Amyloidogenic APP Processing and Tau Phosphorylation: A Mechanistic Link between Glycation and the Development of Alzheimer's Disease

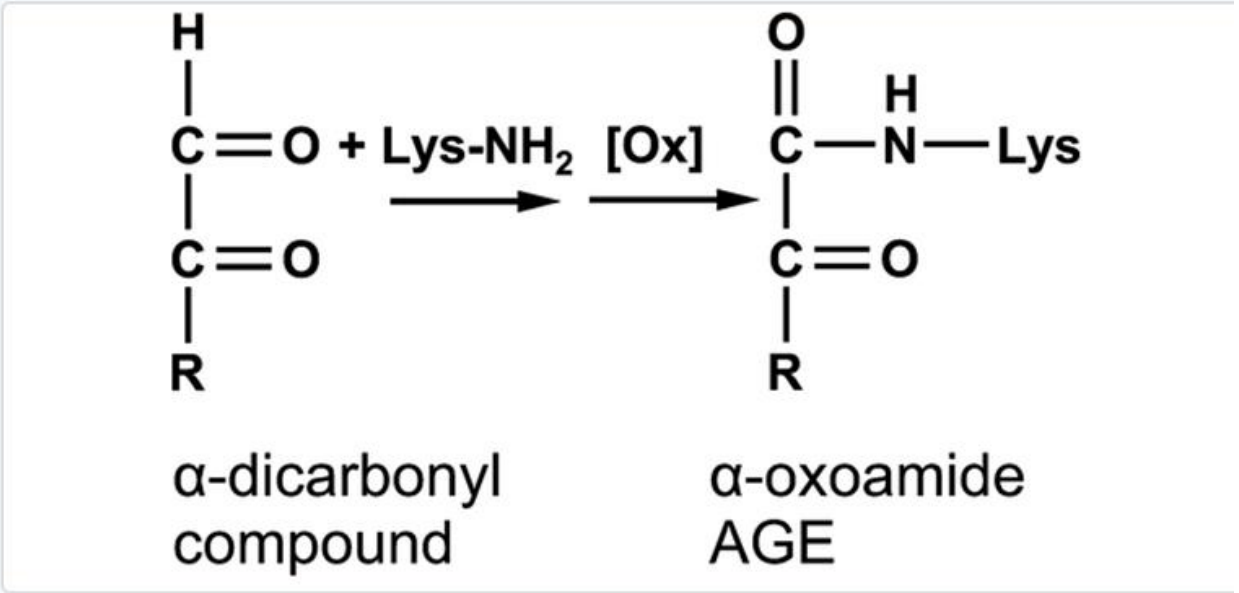
Kedar Batkulwar[†‡], Rashmi Godbole[†], Reema Banarjee[†‡], Omar Kassaar[§], Robert J. Williams[*§], and Mahesh J. Kulkarni[*†‡]



Advanced glycation end products (AGEs) are implicated in the pathology of Alzheimer's disease (AD), as they induce neurodegeneration following interaction with the receptor for AGE (RAGE). This study aimed to establish a mechanistic link between AGE-RAGE signaling and AD pathology. AGE-induced changes in the neuro2a proteome were monitored by SWATH-MS. Western blotting and cell-based reporter assays were used to investigate AGE-RAGE regulated APP processing and tau phosphorylation in primary cortical neurons. Selected protein expression was validated in brain samples affected by AD. The AGE-RAGE axis altered proteome included increased expression of cathepsin B and asparagine endopeptidase (AEP), which mediated an increase in $A\beta_{1-42}$ formation and tau phosphorylation, respectively. Elevated cathepsin B, AEP, RAGE, and pTau levels were found in human AD brain, coincident with enhanced AGEs. This study demonstrates that the AGE-RAGE axis regulates $A\beta_{1-42}$ formation and tau phosphorylation via increased cathepsin B and AEP, providing a new molecular link between AGEs and AD pathology.

Novel α-Oxoamide Advanced-Glycation Endproducts within the N^6-Carboxymethyl Lysine and N^6-Carboxyethyl Lysine Reaction Cascades

Tim Baldensperger[†], Tobias Jost[†], Alexander Zipprich[‡], and Marcus A. Glomb[*†]



The highly reactive α-dicarbonyl compounds glyoxal and methylglyoxal are major precursors of posttranslational protein modifications in vivo. Model incubations of N^2-*t*-Boc-lysine and either glyoxal or methylglyoxal were used to further elucidate the underlying mechanisms of the N^6-carboxymethyl lysine and N^6-carboxyethyl lysine reaction cascades. After independent synthesis of the authentic reference standards, we were able to detect N^6-glyoxylyl lysine and N^6-pyruvoyl lysine for the first time by HPLC-MS^2 analyses. These two novel amide advanced-glycation endproducts were exclusively formed under aerated conditions, suggesting that they were potent markers for oxidative stress. Analogous to the well-known Strecker degradation pathway, leading from amino acids to Strecker acids, the oxidation of an enaminol intermediate is suggested to be the key mechanistic step. A highly sensitive workup for the determination of AGEs in tissues was developed. In support of our hypothesis, the levels of N^6-glyoxylyl lysine and N^6-pyruvoyl lysine in rat livers indeed correlated with liver cirrhosis and aging.

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Therapeutic effects of telomerase in mice with pulmonary fibrosis induced by damage to the lungs and short telomeres

Juan Manuel Povedano, Paula Martinez, Rosa Serrano, Águeda Tejera, Gonzalo Gómez-López, Maria Bobadilla, Juana Maria Flores, Fátima Bosch, Maria A Blasco ✉

Spanish National Cancer Centre, Spain; Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd, Switzerland; EIN, F. Hoffmann-La Roche Ltd, Switzerland; Complutense University of Madrid, Spain; School of Veterinary Medicine, Autonomous University of Barcelona, Spain

Pulmonary fibrosis is a fatal lung disease characterized by fibrotic foci and inflammatory infiltrates. Short telomeres can impair tissue regeneration and are found both in hereditary and sporadic cases. We show here that telomerase expression using AAV9 vectors shows therapeutic effects in a mouse model of pulmonary fibrosis owing to a low-dose bleomycin insult and short telomeres. AAV9 preferentially targets regenerative alveolar type II cells (ATII). AAV9-*Tert*-treated mice show improved lung function and lower inflammation and fibrosis at 1–3 weeks after viral treatment, and improvement or disappearance of the fibrosis at 8 weeks after treatment. AAV9-*Tert* treatment leads to longer telomeres and increased proliferation of ATII cells, as well as lower DNA damage, apoptosis, and senescence. Transcriptome analysis of ATII cells confirms downregulation of fibrosis and inflammation pathways. We provide a proof-of-principle that telomerase activation may represent an effective treatment for pulmonary fibrosis provoked or associated with short telomeres.

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The rate of telomere loss is related to maximum lifespan in birds

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Telomeres are highly conserved regions of DNA that protect the ends of linear chromosomes. The loss of telomeres can signal an irreversible change to a cell's state, including cellular senescence. Senescent cells no longer divide and can damage nearby healthy cells, thus potentially placing them at the crossroads of cancer and ageing. While the epidemiology, cellular and molecular biology of telomeres are well studied, a newer field exploring telomere biology in the context of ecology and evolution is just emerging. With work to date focusing on how telomere shortening relates to individual mortality, less is known about how telomeres relate to ageing rates across species. Here, we investigated telomere length in cross-sectional samples from 19 bird species to determine how rates of telomere loss relate to interspecific variation in maximum lifespan. We found that bird species with longer lifespans lose fewer telomeric repeats each year compared with species with shorter lifespans. In addition, phylogenetic analysis revealed that the rate of telomere loss is evolutionarily conserved within bird families. This suggests that the physiological causes of telomere shortening, or the ability to maintain telomeres, are features that may be responsible for, or co-evolved with, different lifespans observed across species.

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Growing old, yet staying young: The role of telomeres in bats' exceptional longevity

Nicole M. Foley[1], Graham M. Hughes[1], Zixia Huang[1], Michael Clarke[1], David Jebb[1], Conor V. Whelan[1], Eric J. Petit[2], Frédéri...

Abstract

Understanding aging is a grand challenge in biology. Exceptionally long-lived animals have mechanisms that underpin extreme longevity. Telomeres are protective nucleotide repeats on chromosome tips that shorten with cell division, potentially limiting life span. Bats are the longest-lived mammals for their size, but it is unknown whether their telomeres shorten. Using >60 years of cumulative mark-recapture field data, we show that telomeres shorten with age in *Rhinolophus ferrumequinum* and *Miniopterus schreibersii*, but not in the bat genus with greatest longevity, *Myotis*. As in humans, telomerase is not expressed in *Myotis myotis* blood or fibroblasts. Selection tests on telomere maintenance genes show that *ATM* and *SETX*, which repair and prevent DNA damage, potentially mediate telomere dynamics in *Myotis* bats. Twenty-one telomere maintenance genes are differentially expressed in *Myotis*, of which 14 are enriched for DNA repair, and 5 for alternative telomere-lengthening mechanisms. We demonstrate how telomeres, telomerase, and DNA repair genes have contributed to the evolution of exceptional longevity in *Myotis* bats, advancing our understanding of healthy aging.

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Delivery of exogenous mitochondria via centrifugation enhances cellular metabolic function

Mi Jin Kim, Jung Wook Hwang, Chang-Koo Yun, Youngjun Lee & Yong-Soo Choi

Mitochondria are essential organelles involved in the maintenance of cell growth and function, and have been investigated as therapeutic targets in various diseases. Recent studies have demonstrated that direct mitochondrial transfer can restore cellular functions of cells with inherited or acquired mitochondrial dysfunction. However, previous mitochondrial transfer methods are inefficient and time-consuming. Here, we developed a simple and easy mitochondrial transfer protocol using centrifugation, which can be applied to any cell type. By our simple centrifugation method, we found that the isolated mitochondria could be successfully transferred into target cells, including mitochondrial DNA-deleted Rho^0 cells and dexamethasone-treated atrophic muscle cells. We found that mitochondrial transfer normalised ATP production, mitochondrial membrane potential, mitochondrial reactive oxygen species level, and the oxygen consumption rate of the target cells. Furthermore, delivery of intact mitochondria blocked the AMPK/FoxO3/Atrogene pathway underlying muscle atrophy in atrophic muscle cells. Taken together, this simple and rapid mitochondrial transfer method can be used to treat mitochondrial dysfunction-related diseases.

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Small-molecule MDM2 antagonists attenuate the senescence-associated secretory phenotype

Christopher D. Wiley, Nicholas Schaum, Fatouma Alimirah, Jose Alberto Lopez-Dominguez, Arturo V. Orjalo, Gary Scott, Pierre-Yves Desprez, Christopher Benz, Albert R. Davalos ✉ & Judith Campisi ✉

Processes that have been linked to aging and cancer include an inflammatory milieu driven by senescent cells. Senescent cells lose the ability to divide, essentially irreversibly, and secrete numerous proteases, cytokines and growth factors, termed the senescence-associated secretory phenotype (SASP). Senescent cells that lack p53 tumor suppressor function show an exaggerated SASP, suggesting the SASP is negatively controlled by p53. Here, we show that increased p53 activity caused by small molecule inhibitors of MDM2, which promotes p53 degradation, reduces inflammatory cytokine production by senescent cells. Upon treatment with the MDM2 inhibitors nutlin-3a or MI-63, human cells acquired a senescence-like growth arrest, but the arrest was reversible. Importantly, the inhibitors reduced expression of the signature SASP factors IL-6 and IL-1α by cells made senescent by genotoxic stimuli, and suppressed the ability of senescent fibroblasts to stimulate breast cancer cell aggressiveness. Our findings suggest that MDM2 inhibitors could reduce cancer progression in part by reducing the pro-inflammatory environment created by senescent cells.

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Overexpression of PGC-1α in aging muscle enhances a subset of young-like molecular patterns

Sofia Garcia, Nadee Nissanka, Edson A. Mareco, Susana Rossi, Susana Peralta, Francisca Diaz, Richard L. Rotundo, Robson F. Carvalho ✉, Carlos T. Moraes ✉

PGC-1α is a transcriptional co-activator known as the master regulator of mitochondrial biogenesis. Its control of metabolism has been suggested to exert critical influence in the aging process. We have aged mice overexpressing PGC-1α in skeletal muscle to determine whether the transcriptional changes reflected a pattern of expression observed in younger muscle. Analyses of muscle proteins showed that Pax7 and several autophagy markers were increased. In general, the steady-state levels of several muscle proteins resembled that of muscle from young mice. Age-related mtDNA deletion levels were not increased by the PGC-1α-associated increase in mitochondrial biogenesis. Accordingly, age-related changes in the neuromuscular junction were minimized by PGC-1α overexpression. RNA-Seq showed that several genes overexpressed in the aged PGC-1α transgenic are expressed at higher levels in young when compared to aged skeletal muscle. As expected, there was increased expression of genes associated with energy metabolism but also of pathways associated with muscle integrity and regeneration. We also found that PGC-1α overexpression had a mild but significant effect on longevity. Taken together, overexpression of PGC-1α in aged muscle led to molecular changes that resemble the patterns observed in skeletal muscle from younger mice.

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Thymic involution and rising disease incidence with age

Sam Palmer, Luca Albergante, Clare C. Blackburn and T. J. Newman

For many cancer types, incidence rises rapidly with age as an apparent power law, supporting the idea that cancer is caused by a gradual accumulation of genetic mutations. Similarly, the incidence of many infectious diseases strongly increases with age. Here, combining data from immunology and epidemiology, we show that many of these dramatic age-related increases in incidence can be modeled based on immune system decline, rather than mutation accumulation. In humans, the thymus atrophies from infancy, resulting in an exponential decline in T cell production with a half-life of ~16 years, which we use as the basis for a minimal mathematical model of disease incidence. Our model outperforms the power law model with the same number of fitting parameters in describing cancer incidence data across a wide spectrum of different cancers, and provides excellent fits to infectious disease data. This framework provides mechanistic insight into cancer emergence, suggesting that age-related decline in T cell output is a major risk factor.

REVIEWS/COMMENTS/EDITORIALS

The Continuum of Aging and Age-Related Diseases: Common Mechanisms but Different Rates

Claudio Franceschi[1], Paolo Garagnani[2,3,4,5], Cristina Morsiani[2], Maria Conte[2], Aurelia Santoro[2,6*], Andrea Grignolio[7], Daniela Monti[8], Miriam Capri[2,6†] and Stefano Salvioli[2,6†]

Geroscience, the new interdisciplinary field that aims to understand the relationship between aging and chronic age-related diseases (ARDs) and geriatric syndromes (GSs), is based on epidemiological evidence and experimental data that aging is the major risk factor for such pathologies and assumes that aging and ARDs/GSs share a common set of basic biological mechanisms. A consequence is that the primary target of medicine is to combat aging instead of any single ARD/GSs one by one, as favored by the fragmentation into hundreds of specialties and sub-specialties. If the same molecular and cellular mechanisms underpin both aging and ARDs/GSs, a major question emerges: which is the difference, if any, between aging and ARDs/GSs? The hypothesis that ARDs and GSs such as frailty can be conceptualized as accelerated aging will be discussed by analyzing in particular frailty, sarcopenia, chronic obstructive pulmonary disease, cancer, neurodegenerative diseases such as Alzheimer and Parkinson as well as Down syndrome as an example of progeroid syndrome. According to this integrated view, aging and ARDs/GSs become part of a continuum where precise boundaries do not exist and the two extremes are represented by centenarians, who largely avoided or postponed most ARDs/GSs and are characterized by decelerated aging, and patients who suffered one or more severe ARDs in their 60s, 70s, and 80s and show signs of accelerated aging, respectively. In between these two extremes, there is a continuum of intermediate trajectories representing a sort of gray area. Thus, clinically different, classical ARDs/GSs are, indeed, the result of peculiar combinations of alterations regarding the same, limited set of basic mechanisms shared with the aging process. Whether an individual will follow a trajectory of accelerated or decelerated aging will depend on his/her genetic background interacting lifelong with environmental and lifestyle factors. If ARDs and GSs are manifestations of accelerated aging, it is urgent to identify markers capable of distinguishing between biological and chronological age to identify subjects at higher risk of developing ARDs and GSs. To this aim, we propose the use of DNA methylation, N-glycans profiling, and gut microbiota composition to complement the available disease-specific markers.

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Hallmarks of Cellular Senescence

Alejandra Hernandez-Segura, Jamil Nehme, Marco Demaria

Publication stage: In Press Corrected Proof

PlumX Metrics

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Article Info

Highlights

The phenotype associated with cellular senescence is highly variable and heterogeneous.

Senescent cells show common marks, but mechanisms behind these marks are not widely conserved among all the senescence programs.

Lack of universal or program-specific markers is a major limitation for the identification and the targeting of senescent cells *in vitro* and *in vivo*.

Technological advancements or more systematic approaches need to address difficulties associated with the study of cellular senescence.

Cellular senescence is a permanent state of cell cycle arrest that promotes tissue remodeling during development and after injury, but can also contribute to the decline of the regenerative potential and function of tissues, to inflammation, and to tumorigenesis in aged organisms. Therefore, the identification, characterization, and pharmacological elimination of senescent cells have gained attention in the field of aging research. However, the nonspecificity of current senescence markers and the existence of different senescence programs strongly limit these tasks. Here, we describe the molecular regulators of senescence phenotypes and how they are used for identifying senescent cells *in vitro* and *in vivo*. We also highlight the importance that these levels of regulations have in the development of therapeutic targets.

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Cellular senescence: Immunosurveillance and future immunotherapy

Dominick G.A. Burton, Alexandra Stolzing

In response to persistent DNA damage, induction into cell senescence promotes an immunogenic program which facilitates immune clearance of these damaged cells. Under physiological conditions, senescent cells can activate both innate and adaptive immune responses, functioning to maintain tissue homeostasis. In addition, emerging findings suggest that programmed induction of cell senescence may be important for regulating reproductive processes, partly facilitated by immune clearance. However, likely owing to ageing of the immune system, a failure to eliminate senescent cells can contribute to their persistence in tissues, leading to the development and progression of age-related diseases. Such immune failure may in part be due to activation of the senescence program in immune cells, leading to their dysfunction. Furthermore, senescent cells under certain biological contexts have been shown to instead promote immune suppression, a response that may reflect differences between an acute verses chronic senescent phenotype. In this review, we provide an overview of the research to date concerning senescence immunosurviellance, including a focused discussion on the mechanisms by which macrophages may recognise senescent cells. Senescence immunotherapy strategies as an alternative to senolytics for the removal of senescent cells will also be discussed.

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Biochim Biophys Acta. 2018 Mar 7. pii: S0925-4439(18)30080-2. doi: 10.1016/j.bbadis.2018.02.023. [Epub ahead of print]

The yeast replicative aging model.

He C[1], Zhou C[1], Kennedy BK[2].

Author information

Abstract

It has been nearly three decades since the budding yeast Saccharomyces cerevisiae became a significant model organism for aging research and it has emerged as both simple and powerful. The replicative aging assay, which interrogates the number of times a "mother" cell can divide and produce "daughters," has been a stalwart in these studies, and genetic approaches have led to the identification of hundreds of genes impacting lifespan. More recently, cell biological and biochemical approaches have been developed to determine how cellular processes become altered with age. Together, the tools are in place to develop a holistic view of aging in this single-celled organism. Here, we summarize the current state of understanding of yeast replicative aging with a focus on the recent studies that shed new light on how aging pathways interact to modulate lifespan in yeast.

KEYWORDS: Cell asymmetry; Dietary restriction (DR); Mitochondria; Proteostasis; Reactive oxygen species (ROS); Replicative lifespan (RLS); Retrograde response; Ribosomal DNA (rDNA); Sirtuins; Target of rapamycin (TOR); Ubiquitin/proteasome system (UPS); Yeast aging

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The companion dog as a model for human aging and mortality

Jessica M. Hoffman ✉, Kate E. Creevy, Alexander Franks, Dan G. O'Neill, Daniel E. L. Promislow

Around the world, human populations have experienced large increases in average lifespan over the last 150 years, and while individuals are living longer, they are spending more years of life with multiple chronic morbidities. Researchers have used numerous laboratory animal models to understand the biological and environmental factors that influence aging, morbidity, and longevity. However, the most commonly studied animal species, laboratory mice and rats, do not experience environmental conditions similar to those to which humans are exposed, nor do we often diagnose them with many of the naturally occurring pathologies seen in humans. Recently, the companion dog has been proposed as a powerful model to better understand the genetic and environmental determinants of morbidity and mortality in humans. However, it is not known to what extent the age-related dynamics of morbidity, comorbidity, and mortality are shared between humans and dogs. Here, we present the first large-scale comparison of human and canine patterns of age-specific morbidity and mortality. We find that many chronic conditions that commonly occur in human populations (obesity, arthritis, hypothyroidism, and diabetes), and which are associated with comorbidities, are also associated with similarly high levels of comorbidity in companion dogs. We also find significant similarities in the effect of age on disease risk in humans and dogs, with neoplastic, congenital, and metabolic causes of death showing similar age trajectories between the two species. Overall, our study suggests that the companion dog may be an ideal translational model to study the many complex facets of human morbidity and mortality.

OTHER RESEARCH

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High-efficiency RNA-based reprogramming of human primary fibroblasts

Induced pluripotent stem cells (iPSCs) hold great promise for regenerative medicine; however, their potential clinical application is hampered by the low efficiency of somatic cell reprogramming. Here, we show that the synergistic activity of synthetic modified mRNAs encoding reprogramming factors and miRNA-367/302s delivered as mature miRNA mimics greatly enhances the reprogramming of human primary fibroblasts into iPSCs. This synergistic activity is dependent upon an optimal RNA transfection regimen and culturing conditions tailored specifically to human primary fibroblasts. As a result, we can now generate up to 4,019 iPSC colonies from only 500 starting human primary neonatal fibroblasts and reprogram up to 90.7% of individually plated cells, producing multiple sister colonies. This methodology consistently generates clinically relevant, integration-free iPSCs from a variety of human patient's fibroblasts under feeder-free conditions and can be applicable for the clinical translation of iPSCs and studying the biology of reprogramming.

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Description: AU2016305490 (A1) — 2018-03-01

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Method for producing an animal comprising a germline genetic modification

Description of AU2016305490 (A1)

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WO2017024343 (A1)

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WO 2017/024343 PCT/AU2016/050714 1 METHOD FOR PRODUCING AN ANIMAL COMPRISING A GERMLINE GENETIC MODIFICATION FIELD OF THE INVENTION The present invention relates to methods for producing a non-human animal, such as an avian, comprising a targeted germline genetic modification.

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Bibliographic data: WO2018039438 (A1) — 2018-03-01

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INCORPORATION OF UNNATURAL AMINO ACIDS INTO PROTEINS USING BASE EDITING

Page bookmark	WO2018039438 (A1) - INCORPORATION OF UNNATURAL AMINO ACIDS INTO PROTEINS USING BASE EDITING
Inventor(s):	MAIANTI JUAN POBLO [US]; LIU DAVID R [US]; KOBLAN LUKE W [US] +
Applicant(s):	HARVARD COLLEGE [US] +
Classification:	- international: ***C12N15/01; C12N9/22; C12N9/78***
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Application number:	WO2017US48390 20170824 Global Dossier
Priority number(s):	US201662379122P 20160824

Abstract of WO2018039438 (A1)

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Provided herein are systems, compositions, and methods for the incorporation of unnatural amino acids into proteins via nonsense suppression or rare codon suppression. Nonsense codons and rare codons may be introduced into the coding sequence of a protein of interest using a CRISPR/Cas9-based nucleobase editor described herein. The nucleobase editors are able to be programmed by guide nucleotide sequences to edit the target codons in the coding sequence of the protein of interest. Also provided are application enabled by the technology described herein.

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Evolved Cas9 variants with broad PAM compatibility and high DNA specificity

Johnny H. Hu, Shannon M. Miller, Maarten H. Geurts, Weixin Tang, Liwei Chen, Ning Sun, Christina M. Zeina, Xue Gao, Holly A. Rees, Zhi Lin & David R. Liu

A key limitation to the use of CRISPR-Cas9 proteins for genome editing and other applications is the requirement that a protospacer adjacent motif (PAM) be present at the target site. For the most commonly used Cas9 from *Streptococcus pyogenes* (SpCas9), the required PAM sequence is NGG. No natural or engineered Cas9 variants shown to function efficiently in mammalian cells offer a PAM less restrictive than NGG. Here we used phage-assisted continuous evolution (PACE) to evolve an expanded PAM SpCas9 variant (xCas9) that can recognize a broad range of PAM sequences including NG, GAA, and GAT. The PAM compatibility of xCas9 is the broadest reported to date among Cas9s active in mammalian cells, and supports applications in human cells including targeted transcriptional activation, nuclease-mediated gene disruption, and both cytidine and adenine base editing. Remarkably, despite its broadened PAM compatibility, xCas9 has much greater DNA specificity than SpCas9, with substantially lower genome-wide off-target activity at all NGG target sites tested, as well as minimal off-target activity when targeting genomic sites with non-NGG PAMs. These findings expand the DNA targeting scope of CRISPR systems and establish that there is no necessary trade-off between Cas9 editing efficiency, PAM compatibility, and DNA specificity.

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Mol Cell. 2018 Mar 1;69(5):893-905.e7. doi: 10.1016/j.molcel.2018.01.032.

CRISPR RNA-Dependent Binding and Cleavage of Endogenous RNAs by the Campylobacter jejuni Cas9.

Dugar G[1], Leenay RT[2], Eisenbart SK[1], Bischler T[1], Aul BU[1], Beisel CL[3], Sharma CM[4].

Author information

Abstract

Cas9 nucleases naturally utilize CRISPR RNAs (crRNAs) to silence foreign double-stranded DNA. While recent work has shown that some Cas9 nucleases can also target RNA, RNA recognition has required nuclease modifications or accessory factors. Here, we show that the Campylobacter jejuni Cas9 (CjCas9) can bind and cleave complementary endogenous mRNAs in a crRNA-dependent manner. Approximately 100 transcripts co-immunoprecipitated with CjCas9 and generally can be subdivided through their base-pairing potential to the four crRNAs. A subset of these RNAs was cleaved around or within the predicted binding site. Mutational analyses revealed that RNA binding was crRNA and tracrRNA dependent and that target RNA cleavage required the CjCas9 HNH domain. We further observed that RNA cleavage was PAM independent, improved with greater complementarity between the crRNA and the RNA target, and was programmable in vitro. These findings suggest that C. jejuni Cas9 is a promiscuous nuclease that can coordinately target both DNA and RNA.

KEYWORDS: CRISPR; Campylobacter jejuni; Cas9; RIP-seq; RNA binding proteins; RNA cleavage; crRNA; genome editing; non-coding RNA; post-transcriptional regulation

United States Patent Application *20180066258*
Kind Code **A1**
Powell; Michael J **March 8, 2018**

SPECIFIC SYNTHETIC CHIMERIC XENONUCLEIC ACID GUIDE RNA; s(XNA-gRNA) FOR ENHANCING CRISPR MEDIATED GENOME EDITING EFFICIENCY

Abstract

The invention provides specific synthetic chimeric xenonucleic acid guide RNA; s(XNA-gRNA) for enhancing crispr mediated genome editing efficiency. The invention also provides methods and compositions for inducing CRISPR/Cas-based gene editing/regulation (e.g., genome editing or gene expression) of a target nucleic acid (e.g., target DNA or target RNA) in a cell. The methods include using single guide RNAs (sgRNAs) that have been chemically modified with xeno nucleic acids which enhance gene regulation of the target nucleic acid in a primary cell for use in ex vivo therapy or in a cell in a subject for use in in vivo therapy. Additionally, provided herein are methods for preventing or treating a genetic disease in a subject by administering a sufficient amount of a sgRNA that has been chemically modified with xeno nucleic acids to correct a mutation in a target gene associated with the genetic disease.

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