Heales
HEALTHY LIFE EXTENSION SOCIETY

Scientific News
5th of June 2016
Sven Bulterijs

“Latest Aging Research Updates” Facebook group is now public!

Heales
HEALTHY LIFE EXTENSION SOCIETY

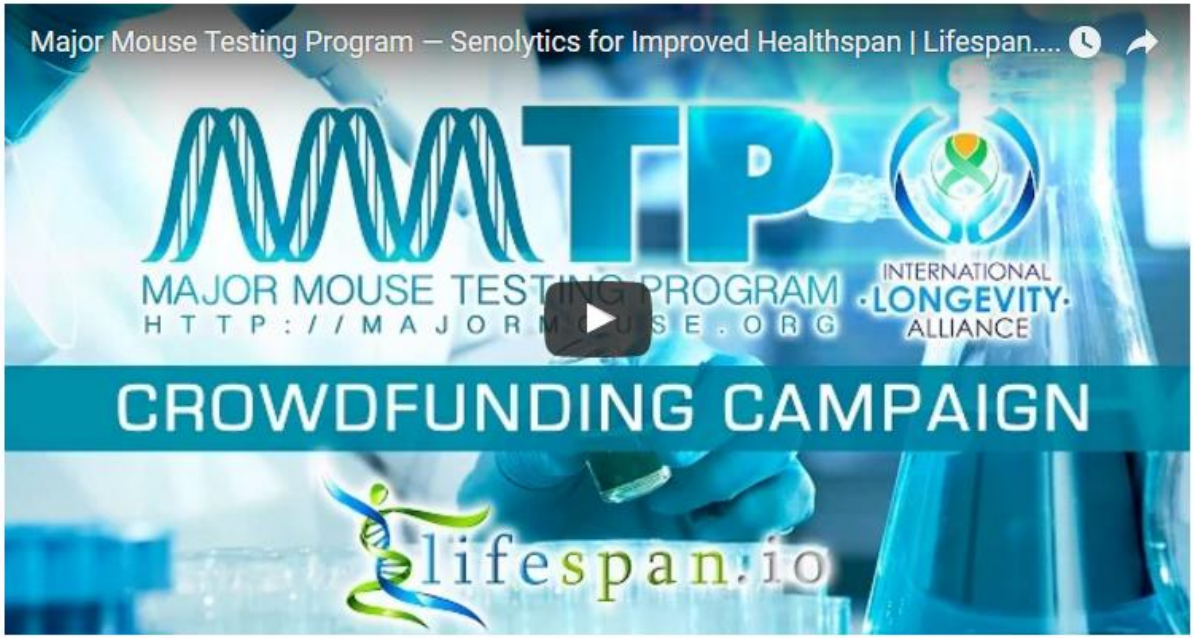
THE MAJOR MOUSE TESTING PROGRAM

Testing a new class of compounds, Senolytics, on their ability to extend healthy lifespan by clearing out dysfunctional cells in the body.

BY DR. ALEXANDRA STOLZING

OVERVIEW | UPDATES | COMMENTS | BACKERS

SEARCH



$33,135
PLEDGED OF $45,000 GOAL

277 BACKERS

19 DAYS TO GO

CONTRIBUTE NOW

Flexible Funding: All funds this campaign raises will be collected.

Heales
HEALTHY LIFE EXTENSION SOCIETY

First Rise in U.S. Death Rate in Years Surprises Experts

By SABRINA TAVERNISE JUNE 1, 2016

Paramedics in Portland, Me., responded to a call of a heroin overdose last year.
Derek Davis/Portland Press Herald, via Getty Images

Mortality increases for

- Alzheimer disease
- Chronic lower respiratory diseases (COPD)
- Drug overdose
- Homicide
- Hypertension
- Liver disease
- Parkinson’s disease
- Septicemia
- Stroke
- Suicide

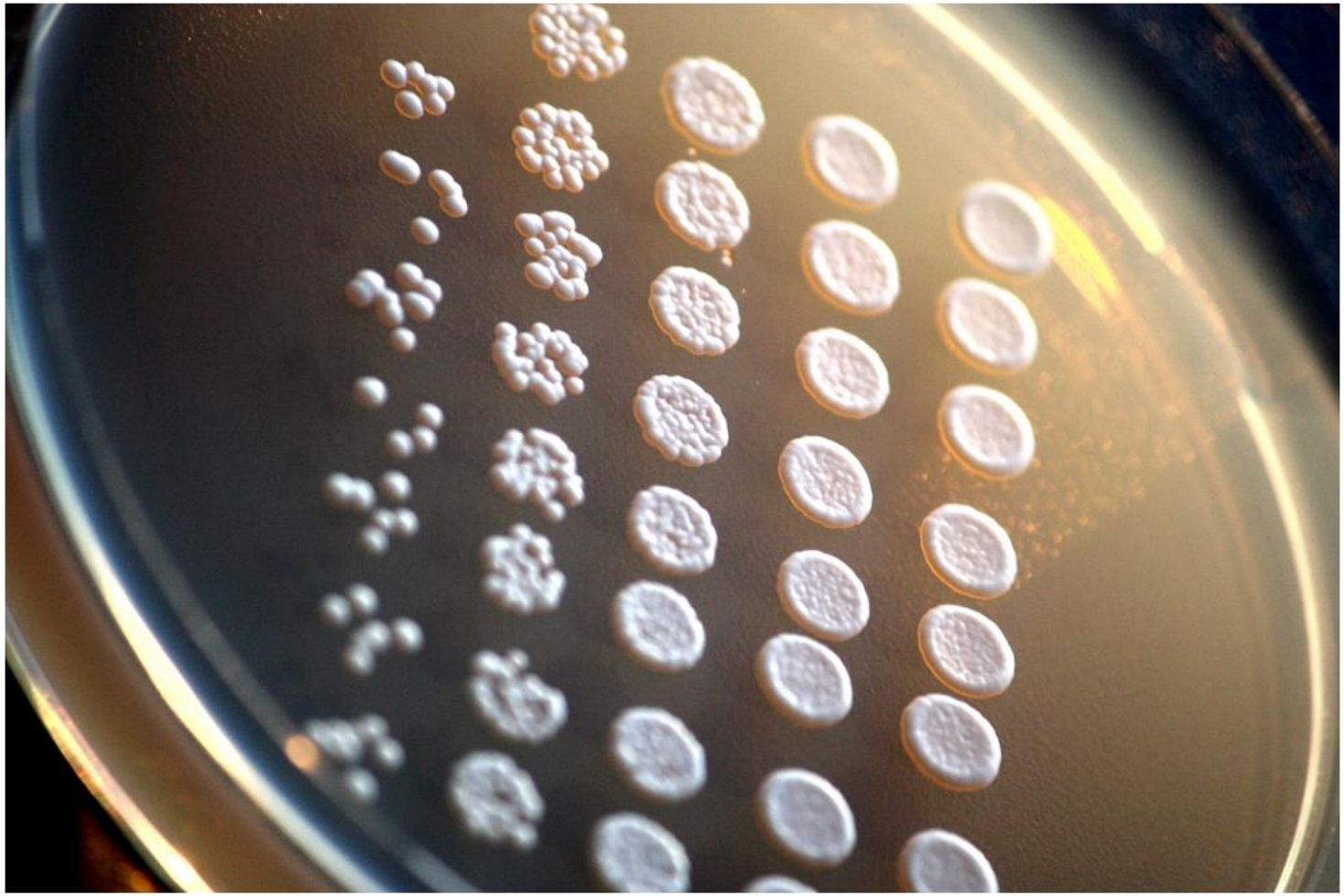
Heales
HEALTHY LIFE EXTENSION SOCIETY

Yeast longevity promoted by reversing aging-associated decline in heavy isotope content

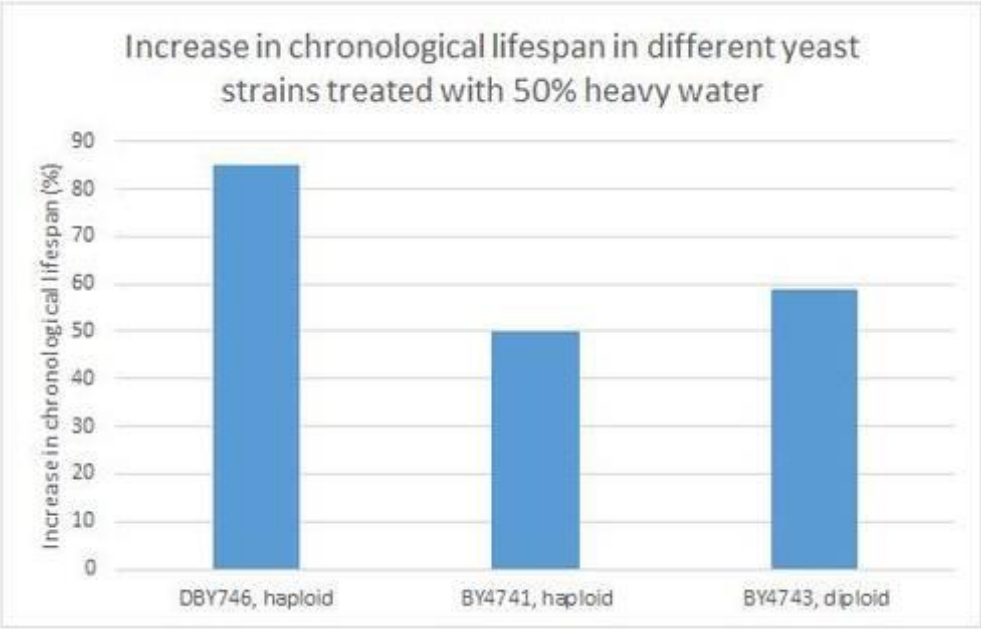
Dysregulation of metabolism develops with organismal aging. Both genetic and environmental manipulations promote longevity by effectively diverting various metabolic processes against aging. How these processes converge on the metabolome is not clear. Here we report that the heavy isotopic forms of common elements, a universal feature of metabolites, decline in yeast cells undergoing chronological aging. Supplementation of deuterium, a heavy hydrogen isotope, through heavy water (D_2O) uptake extends yeast chronological lifespan (CLS) by up to 85% with minimal effects on growth. The CLS extension by D_2O bypasses several known genetic regulators, but is abrogated by calorie restriction and mitochondrial deficiency. Heavy water substantially suppresses endogenous generation of reactive oxygen species (ROS) and slows the pace of metabolic consumption and disposal. Protection from aging by heavy isotopes might result from kinetic modulation of biochemical reactions. Altogether, our findings reveal a novel perspective of aging and new means for promoting longevity.

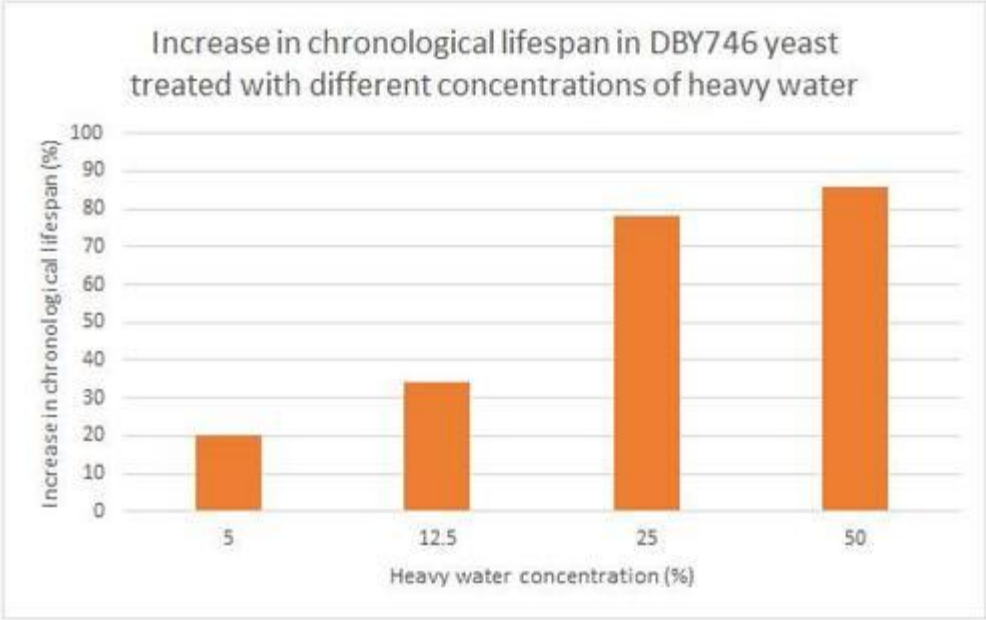
Heales
HEALTHY LIFE EXTENSION SOCIETY

Heavy Water Extends Yeast Lifespan



Heales
HEALTHY LIFE EXTENSION SOCIETY





Heales
HEALTHY LIFE EXTENSION SOCIETY

Effect of Calorie Restriction on Mood, Quality of Life, Sleep, and Sexual Function in Healthy Nonobese Adults

The CALERIE 2 Randomized Clinical Trial ONLINE FIRST

Interventions Two years of 25% CR or AL.

Main Outcomes and Measures Self-report questionnaires were administered to measure mood (Beck Depression Inventory-II [BDI-II], score range 0-63, higher scores indicating worse mood, and Profile of Mood States [POMS], with a total mood disturbance score range of −32 to 200 and higher scores indicating higher levels of the constructs measured), QOL (Rand 36-Item Short Form, score range 0-100, higher scores reflecting better QOL, and Perceived Stress Scale, score range 0-40, higher scores indicating higher levels of stress), sleep (Pittsburgh Sleep Quality Index [PSQI], total score range 0-21, higher scores reflecting worse sleep quality), and sexual function (Derogatis Interview for Sexual Function–Self–report, total score range 24-188, higher scores indicating better sexual functioning).

Results In all, 218 participants (152 women [69.7%]; mean [SD] age, 37.9 (7.2) years; mean [SD] BMI, 25.1 [1.6]) were included in the analyses. The CR and AL groups lost a mean (SE) of 7.6 (0.3) kg and 0.4 (0.5) kg, respectively, at month 24 ($P < .001$). Compared with the AL group, the CR group had significantly improved mood (BDI-II: between-group difference [BGD], −0.76; 95% CI, −1.41 to −0.11; effect size [ES], −0.35), reduced tension (POMS: BGD, −0.79; 95% CI, −1.38 to −0.19; ES, −0.39), and improved general health (BGD, 6.45; 95% CI, 3.93 to 8.98; ES, 0.75) and sexual drive and relationship (BGD, 1.06; 95% CI, 0.11 to 2.01; ES, 0.35) at month 24 as well as improved sleep duration at month 12 (BGD, −0.26; 95% CI, −0.49 to −0.02; ES, −0.32) (all $P < .05$). Greater percent weight loss in the CR group at month 24 was associated with increased vigor (Spearman correlation coefficient, $\rho = -0.30$) and less mood disturbance ($\rho = 0.27$) measured with the POMS, improved general health ($\rho = -0.27$) measured with the SF-36, and better sleep quality per the PSQI total score ($\rho = 0.28$) (all $P < .01$).

Conclusions and Relevance In nonobese adults, CR had some positive effects and no negative effects on health-related QOL.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Generation of mice with longer and better preserved telomeres in the absence of genetic manipulations

Elisa Varela, Miguel A. Muñoz-Lorente, Agueda M. Tejera, Sagrario Ortega & Maria A. Blasco

Although telomere length is genetically determined, mouse embryonic stem (ES) cells with telomeres of twice the normal size have been generated. Here, we use such ES cells with 'hyper-long' telomeres, which also express green fluorescent protein (GFP), to generate chimaeric mice containing cells with both hyper-long and normal telomeres. We show that chimaeric mice contain GFP-positive cells in all mouse tissues, display normal tissue histology and normal survival. Both hyper-long and normal telomeres shorten with age, but GFP-positive cells retain longer telomeres as mice age. Chimaeric mice with hyper-long telomeres also accumulate fewer cells with short telomeres and less DNA damage with age, and express lower levels of p53. In highly renewing compartments, such as the blood, cells with hyper-long telomeres are longitudinally maintained or enriched with age. We further show that wound-healing rates in the skin are increased in chimaeric mice. Our work demonstrates that mice with functional, longer and better preserved telomeres can be generated without the need for genetic manipulations, such as *TERT* overexpression.

Danazol Treatment for Telomere Diseases

RESULTS

After 27 patients were enrolled, the study was halted early, because telomere attrition was reduced in all 12 patients who could be evaluated for the primary end point; in the intention-to-treat analysis, 12 of 27 patients (44%; 95% confidence interval [CI], 26 to 64) met the primary efficacy end point. Unexpectedly, almost all the patients (11 of 12, 92%) had a gain in telomere length at 24 months as compared with baseline (mean increase, 386 bp [95% CI, 178 to 593]); in exploratory analyses, similar increases were observed at 6 months (16 of 21 patients; mean increase, 175 bp [95% CI, 79 to 271]) and 12 months (16 of 18 patients; mean increase, 360 bp [95% CI, 209 to 512]). Hematologic responses occurred in 19 of 24 patients (79%) who could be evaluated at 3 months and in 10 of 12 patients (83%) who could be evaluated at 24 months. Known adverse effects of danazol — elevated liver-enzyme levels and muscle cramps — of grade 2 or less occurred in 41% and 33% of the patients, respectively.

Full Text of Results...

CONCLUSIONS

In our study, treatment with danazol led to telomere elongation in patients with telomere diseases. (Funded by the National Institutes of Health; ClinicalTrials.gov number, NCT01441037.)

Heales
HEALTHY LIFE EXTENSION SOCIETY

Decades of field data reveal that turtles senesce in the wild

Daniel A. Warner[a,1], David A. W. Miller[b], Anne M. Bronikowski[a], and Fredric J. Janzen[a,2]

Lifespan and aging rates vary considerably across taxa; thus, understanding the factors that lead to this variation is a primary goal in biology and has ramifications for understanding constraints and flexibility in human aging. Theory predicts that senescence—declining reproduction and increasing mortality with advancing age—evolves when selection against harmful mutations is weaker at old ages relative to young ages or when selection favors pleiotropic alleles with beneficial effects early in life despite late-life costs. However, in many long-lived ectotherms, selection is expected to remain strong at old ages because reproductive output typically increases with age, which may lead to the evolution of slow or even negligible senescence. We show that, contrary to current thinking, both reproduction and survival decline with adult age in the painted turtle, *Chrysemys picta*, based on data spanning >20 y from a wild population. Older females, despite relatively high reproductive output, produced eggs with reduced hatching success. Additionally, age-specific mark–recapture analyses revealed increasing mortality with advancing adult age. These findings of reproductive and mortality senescence challenge the contention that chelonians do not age and more generally provide evidence of reduced fitness at old ages in nonmammalian species that exhibit long chronological lifespans.

Age-Related Accumulation of Somatic Mitochondrial DNA Mutations in Adult-Derived Human iPSCs

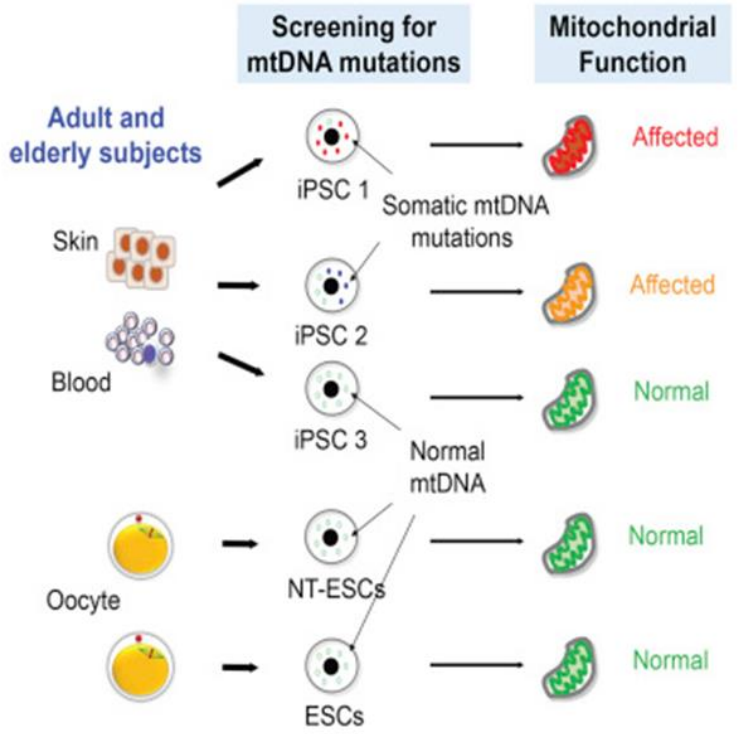
Highlights

- Human iPSC clones derived from elderly adults show accumulation of mtDNA mutations
- Fewer mtDNA mutations are present in ESCs and iPSCs derived from younger adults
- Accumulated mtDNA mutations can impact metabolic function in iPSCs

Summary

The genetic integrity of iPSCs is an important consideration for therapeutic application. In this study, we examine the accumulation of somatic mitochondrial genome (mtDNA) mutations in skin fibroblasts, blood, and iPSCs derived from young and elderly subjects (24–72 years). We found that pooled skin and blood mtDNA contained low heteroplasmic point mutations, but a panel of ten individual iPSC lines from each tissue or clonally expanded fibroblasts carried an elevated load of heteroplasmic or homoplasmic mutations, suggesting that somatic mutations randomly arise within individual cells but are not detectable in whole tissues. The frequency of mtDNA defects in iPSCs increased with age, and many mutations were non-synonymous or resided in RNA coding genes and thus can lead to respiratory defects. Our results highlight a need to monitor mtDNA mutations in iPSCs, especially those generated from older patients, and to examine the metabolic status of iPSCs destined for clinical applications.

Graphical Abstract



Repression of the Antioxidant NRF2 Pathway in Premature Aging

Nard Kubben, Weiqi Zhang[8], Lixia Wang, Ty C. Voss, Jiping Yang, Jing Qu[8], Guang-Hui Liu, Tom Misteli

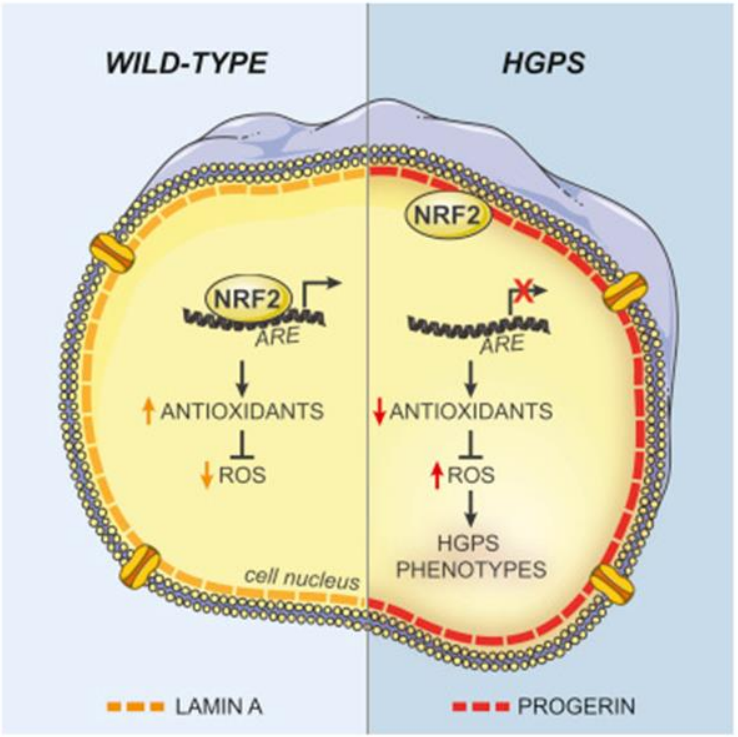
Highlights

- Impaired activity of the NRF2 antioxidative pathway is a driver mechanism in HGPS
- Suppressed NRF2 activity and oxidative stress recapitulate HGPS aging defects
- Reactivation of NRF2 decreases oxidative stress and reverses cellular HGPS defects

Summary

Hutchinson-Gilford progeria syndrome (HGPS) is a rare, invariably fatal premature aging disorder. The disease is caused by constitutive production of progerin, a mutant form of the nuclear architectural protein lamin A, leading, through unknown mechanisms, to diverse morphological, epigenetic, and genomic damage and to mesenchymal stem cell (MSC) attrition in vivo. Using a high-throughput siRNA screen, we identify the NRF2 antioxidant pathway as a driver mechanism in HGPS. Progerin sequesters NRF2 and thereby causes its subnuclear mislocalization, resulting in impaired NRF2 transcriptional activity and consequently increased chronic oxidative stress. Suppressed NRF2 activity or increased oxidative stress is sufficient to recapitulate HGPS aging defects, whereas reactivation of NRF2 activity in HGPS patient cells reverses progerin-associated nuclear aging defects and restores in vivo viability of MSCs in an animal model. These findings identify repression of the NRF2-mediated antioxidative response as a key contributor to the premature aging phenotype.

Graphical Abstract



Heales
HEALTHY LIFE EXTENSION SOCIETY

Modulation of leukotriene B_4 receptor 1 signaling by receptor for advanced glycation end products (RAGE)

Leukotriene B_4 (LTB_4) receptor 1 (BLT1), a high-affinity GPCR for LTB_4, plays important roles in acute and chronic inflammatory diseases. Although the LTB_4–BLT1 axis is known to promote inflammation, no studies have defined the binding proteins that modulate LTB_4–BLT1 signaling. In this study, the receptor for advanced glycation end products (RAGE) interacted with BLT1 in human cervical epithelial HeLa cells. RAGE increased LTB_4–BLT1–dependent ERK phosphorylation and inhibited LTB_4–BLT1–dependent activation of NF-κB and up-regulation of proinflammatory cytokines and chemokines. RAGE-dependent inhibition of NF-κB was blunted by treatment with an MEK inhibitor, suggesting that RAGE suppresses LTB_4–BLT1–dependent NF-κB signaling by enhancing the MEK–ERK pathway. Meanwhile, in a chemotaxis assay of mouse bone marrow-derived neutrophils, the velocity of LTB_4–dependent neutrophil migration was attenuated by soluble RAGE, which is an inhibitory decoy protein for RAGE signaling, in a dose-dependent manner (0.2–5 μg/ml), or by RAGE deficiency. Furthermore, both LTB_4–dependent ERK phosphorylation in neutrophils and LTB_4–dependent neutrophil accumulation in a murine peritonitis model were significantly attenuated in RAGE-deficient mice compared with C57BL/6J wild-type mice, indicating that RAGE potentiates LTB_4–dependent neutrophil migration by enhancing ERK phosphorylation. Our results demonstrate that RAGE interacts with BLT1 and modulates LTB_4–BLT1 signaling through potentiation of the MEK–ERK pathway.—Ichiki, T., Koga, T., Okuno, T., Saeki K., Yamamoto, Y., Yamamoto, H., Sakaguchi, M., Yokomizo, T. Modulation of leukotriene B_4 receptor 1 signaling by receptor for advanced glycation end products (RAGE).

Heales
HEALTHY LIFE EXTENSION SOCIETY

Selective sorting and destruction of mitochondrial membrane proteins in aged yeast

Adam L Hughes ✉, Casey E Hughes, Kiersten A Henderson, Nina Yazvenko, Daniel E Gottschling ✉

Mitochondrial dysfunction is a hallmark of aging, and underlies the development of many diseases. Cells maintain mitochondrial homeostasis through a number of pathways that remodel the mitochondrial proteome or alter mitochondrial content during times of stress or metabolic adaptation. Here, using yeast as a model system, we identify a new mitochondrial degradation system that remodels the mitochondrial proteome of aged cells. Unlike many common mitochondrial degradation pathways, this system selectively removes a subset of membrane proteins from the mitochondrial inner and outer membranes, while leaving the remainder of the organelle intact. Selective removal of preexisting proteins is achieved by sorting into a mitochondrial-derived compartment, or MDC, followed by release through mitochondrial fission and elimination by autophagy. Formation of MDCs requires the import receptors Tom70/71, and failure to form these structures exacerbates preexisting mitochondrial dysfunction, suggesting that the MDC pathway provides protection to mitochondria in times of stress.

Heales
HEALTHY LIFE EXTENSION SOCIETY

J Gerontol A Biol Sci Med Sci. 2016 May 6. pii: glw074. [Epub ahead of print]

Exome-wide Association Study Identifies CLEC3B Missense Variant p.S106G as Being Associated With Extreme Longevity in East Asian Populations.

Tanisawa K[1], Arai Y[2], Hirose N[2], Shimokata H[3], Yamada Y[4], Kawai H[5], Kojima M[5], Obuchi S[5], Hirano H[6], Yoshida H[6], Suzuki H[7], Fujiwara Y[7], Ihara K[8], Sugaya M[9], Arai T[10], Mori S[11], Sawabe M[12], Sato N[13], Muramatsu M[13], Higuchi M[14], Liu YW[15], Kong QP[15], Tanaka M[16].

⊕ Author information

Abstract

Life span is a complex trait regulated by multiple genetic and environmental factors; however, the genetic determinants of extreme longevity have been largely unknown. To identify the functional coding variants associated with extreme longevity, we performed an exome-wide association study (EWAS) on a Japanese population by using an Illumina HumanExome Beadchip and a focused replication study on a Chinese population. The EWAS on two independent Japanese cohorts consisting of 530 nonagenarians/centenarians demonstrated that the G allele of CLEC3B missense variant p.S106G was associated with extreme longevity at the exome-wide level of significance ($p = 2.33\times10^{-7}$, odds ratio [OR] = 1.50). The CLEC3B gene encodes tetranectin, a protein implicated in the mineralization process in osteogenesis as well as in the prognosis and metastasis of cancer. The replication study consisting of 448 Chinese nonagenarians/centenarians showed that the G allele of CLEC3B p.S106G was also associated with extreme longevity ($p = .027$, OR = 1.51), and the p value of this variant reached 1.87×10^{-8} in the meta-analysis of Japanese and Chinese populations. In conclusion, the present study identified the CLEC3B p.S106G as a novel longevity-associated variant, raising the novel hypothesis that tetranectin, encoded by CLEC3B, plays a role in human longevity and aging.

Mosaic Loss of Chromosome Y in Blood Is Associated with Alzheimer Disease

Jan P. Dumanski, Jean-Charles Lambert, Chiara Rasi, Vilmantas Giedraitis, Hanna Davies, Benjamin Grenier-Boley, Cecilia M. Lindgren, Dominique Campion, Carole Dufouil, The European Alzheimer's Disease Initiative Investigators, Florence Pasquier, Philippe Amouyel, Lars Lannfelt, Martin Ingelsson, Lena Kilander, Lars Lind, Lars A. Forsberg

Men have a shorter life expectancy compared with women but the underlying factor(s) are not clear. Late-onset, sporadic Alzheimer disease (AD) is a common and lethal neurodegenerative disorder and many germline inherited variants have been found to influence the risk of developing AD. Our previous results show that a fundamentally different genetic variant, i.e., lifetime-acquired loss of chromosome Y (LOY) in blood cells, is associated with all-cause mortality and an increased risk of non-hematological tumors and that LOY could be induced by tobacco smoking. We tested here a hypothesis that men with LOY are more susceptible to AD and show that LOY is associated with AD in three independent studies of different types. In a case-control study, males with AD diagnosis had higher degree of LOY mosaicism (adjusted odds ratio = 2.80, p = 0.0184, AD events = 606). Furthermore, in two prospective studies, men with LOY at blood sampling had greater risk for incident AD diagnosis during follow-up time (hazard ratio [HR] = 6.80, 95% confidence interval [95% CI] = 2.16–21.43, AD events = 140, p = 0.0011). Thus, LOY in blood is associated with risks of both AD and cancer, suggesting a role of LOY in blood cells on disease processes in other tissues, possibly via defective immunosurveillance. As a male-specific risk factor, LOY might explain why males on average live shorter lives than females.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Aging (Albany NY). 2016 May 7. [Epub ahead of print]

Sensitivity of primary fibroblasts in culture to atmospheric oxygen does not correlate with species lifespan.

Patrick A[1], Seluanov M[1], Hwang C[1], Tam J[1], Khan T[1], Morgenstern A[1], Wiener L[1], Vazquez JM[1], Zafar H[1], Wen R[1], Muratkalyeva M[1], Doerig K[1], Zagorulya M[1], Cole L[1], Catalano S[1], Ladd AA[2], Coppi AA[3], Coşkun Y[4], Tian X[1], Ablaeva J[1], Nevo E[5], Gladyshev VN[6], Zhang ZD[7], Vijg J[7], Seluanov A[1], Gorbunova V[1].

⊕ Author information

Abstract

Differences in the way human and mouse fibroblasts experience senescence in culture had long puzzled researchers. While senescence of human cells is mediated by telomere shortening, Parrinello et al. demonstrated that senescence of mouse cells is caused by extreme oxygen sensitivity. It was hypothesized that the striking difference in oxygen sensitivity between mouse and human cells explains their different rates of aging. To test if this hypothesis is broadly applicable, we cultured cells from 16 rodent species with diverse lifespans in 3% and 21% oxygen and compared their growth rates. Unexpectedly, fibroblasts derived from laboratory mouse strains were the only cells demonstrating extreme sensitivity to oxygen. Cells from hamster, muskrat, woodchuck, capybara, blind mole rat, paca, squirrel, beaver, naked mole rat and wild-caught mice were mildly sensitive to oxygen, while cells from rat, gerbil, deer mouse, chipmunk, guinea pig and chinchilla showed no difference in the growth rate between 3% and 21% oxygen. We conclude that, although the growth of primary fibroblasts is generally improved by maintaining cells in 3% oxygen, the extreme oxygen sensitivity is a peculiarity of laboratory mouse strains, possibly related to their very long telomeres, and fibroblast oxygen sensitivity does not directly correlate with species' lifespan.

Heales
HEALTHY LIFE EXTENSION SOCIETY

J Transl Sci. 2016;2(3):185-187. Epub 2016 Apr 28.

The bright side of reactive oxygen species: lifespan extension without cellular demise.

Maiese K[1].

Author information

Abstract

Oxidative stress and the generation of reactive oxygen species (ROS) can lead to mitochondrial dysfunction, DNA damage, protein misfolding, programmed cell death with apoptosis and autophagy, and the promotion of aging -dependent processes. Mitochondria control the processing of redox energy that yields adenosine triphosphate (ATP) through the oxidation of glucose, pyruvate, and nicotinamide adenine dinucleotide. Ultimately, the generation of ROS occurs with the aerobic production of ATP. Although reduced levels of ROS may lead to tolerance against metabolic, mechanical, and oxidative stressors and the generation of brief periods of ROS during ischemia-reperfusion models may limit cellular injury, under most circumstances ROS and mitochondrial dysfunction can lead to apoptotic caspase activation and autophagy induction that can result in cellular demise. Yet, new work suggests that ROS generation may have a positive impact through respiratory complex I reverse electron transport that can extend lifespan. Such mechanisms may bring new insight into clinically relevant disorders that are linked to cellular senescence and aging of the body's system. Further investigation of the potential "bright side" of ROS and mitochondrial respiration is necessary to target specific pathways, such as the mechanistic target of rapamycin, nicotinamidases, sirtuins, mRNA decoupling and protein expression, and Wnt signaling, that can impact oxidative stress-ROS mechanisms to extend lifespan and eliminate disease onset.

Heales
HEALTHY LIFE EXTENSION SOCIETY

J Gerontol A Biol Sci Med Sci. 2016 May 21. pii: glw088. [Epub ahead of print]

Enhanced Cognition and Hypoglutamatergic Signaling in a Growth Hormone Receptor Knockout Mouse Model of Successful Aging.

Hascup KN[1], Lynn MK[2], Fitzgerald PJ[1], Randall S[1], Kopchick JJ[3], Boger HA[4], Bartke A[5], Hascup ER[6].

Author information

Abstract

Growth hormone receptor knockout (GHR-KO) mice are long lived with improved health span, making this an excellent model system for understanding biochemical mechanisms important to cognitive reserve. The purpose of the present study was to elucidate differences in cognition and glutamatergic dynamics between aged (20- to 24-month-old) GHR-KO and littermate controls. Glutamate plays a critical role in hippocampal learning and memory and is implicated in several neurodegenerative disorders, including Alzheimer's disease. Spatial learning and memory were assessed using the Morris water maze (MWM), whereas independent dentate gyrus (DG), CA3, and CA1 basal glutamate, release, and uptake measurements were conducted in isoflurane anesthetized mice utilizing an enzyme-based microelectrode array (MEA) coupled with constant potential amperometry. These MEAs have high temporal and low spatial resolution while causing minimal damage to the surrounding parenchyma. Littermate controls performed worse on the memory portion of the MWM behavioral task and had elevated DG, CA3, and CA1 basal glutamate and stimulus-evoked release compared with age-matched GHR-KO mice. CA3 basal glutamate negatively correlated with MWM performance. These results support glutamatergic regulation in learning and memory and may have implications for therapeutic targets to delay the onset of, or reduce cognitive decline, in Alzheimer's disease.

REVIEWS/COMMENTS/EDITORIALS

Gastrointestinal Microbiota and Their Contribution to Healthy Aging

Mello A.M.[a] · Paroni G.[b] · Daragjati J.[c] · Pilotto A.[a]

Studies on populations at different ages have shown that after birth, the gastrointestinal (GI) microbiota composition keeps evolving, and this seems to occur especially in old age. Significant changes in GI microbiota composition in older subjects have been reported in relation to diet, drug use and the settings where the older subjects are living, that is, in community nursing homes or in a hospital. Moreover, changes in microbiota composition in the old age have been related to immunosenescence and inflammatory processes that are pathophysiological mechanisms involved in the pathways of frailty. Frailty is an age-related condition of increased vulnerability to stresses due to the impairment in multiple inter-related physiologic systems that are associated with an increased risk of adverse outcomes, such as falls, delirium, institutionalization, hospitalization and death. Preliminary data suggest that changes in microbiota composition may contribute to the variations in the biological, clinical, functional and psycho-social domains that occur in the frail older subjects. Multidimensional evaluation tools based on a Comprehensive Geriatric Assessment (CGA) have demonstrated to be useful in identifying and measuring the severity of frailty in older subjects. Thus, a CGA approach should be used more widely in clinical practice to evaluate the multidimensional effects potentially related to GI microbiota composition of the older subjects. Probiotics have been shown to be effective in restoring the microbiota changes of older subjects, promoting different aspects of health in elderly people as improving immune function and reducing inflammation. Whether modulation of GI microbiota composition, with multi-targeted interventions, could have an effect on the prevention of frailty remains to be further investigated in the perspective of improving the health status of frail 'high risk' older individuals.

Heales
HEALTHY LIFE EXTENSION SOCIETY

J Gerontol A Biol Sci Med Sci. 2016 May 21. pii: glw090. [Epub ahead of print]

Rapamycin: An InhibiTOR of Aging Emerges From the Soil of Easter Island.

Arriola Apelo SI[1], Lamming DW[2].

Author information

Abstract

Rapamycin (sirolimus) is a macrolide immunosuppressant that inhibits the mechanistic target of rapamycin (mTOR) protein kinase and extends lifespan in model organisms including mice. Although rapamycin is an FDA-approved drug for select indications, a diverse set of negative side effects may preclude its wide-scale deployment as an antiaging therapy. mTOR forms two different protein complexes, mTORC1 and mTORC2; the former is acutely sensitive to rapamycin whereas the latter is only chronically sensitive to rapamycin in vivo. Over the past decade, it has become clear that although genetic and pharmacological inhibition of mTORC1 extends lifespan and delays aging, inhibition of mTORC2 has negative effects on mammalian health and longevity and is responsible for many of the negative side effects of rapamycin. In this review, we discuss recent advances in understanding the molecular and physiological effects of rapamycin treatment, and we discuss how the use of alternative rapamycin treatment regimens or rapamycin analogs has the potential to mitigate the deleterious side effects of rapamycin treatment by more specifically targeting mTORC1. Although the side effects of rapamycin are still of significant concern, rapid progress is being made in realizing the revolutionary potential of rapamycin-based therapies for the treatment of diseases of aging.

DNA, the central molecule of aging

Understanding the molecular mechanism of aging could have enormous medical implications. Despite a century of research, however, there is no universally accepted theory regarding the molecular basis of aging. On the other hand, there is plentiful evidence suggesting that DNA constitutes the central molecule in this process. Here, we review the roles of chromatin structure, DNA damage, and shortening of telomeres in aging and propose a hypothesis for how their interplay leads to aging phenotypes.

Biochim Biophys Acta. 2016 May 8. pii: S0925-4439(16)30113-2. doi: 10.1016/j.bbadis.2016.05.005. [Epub ahead of print]

Cellular mechanisms and consequences of glycation in atherosclerosis and obesity.

López-Díez R[1], Shekhtman A[2], Ramasamy R[1], Schmidt AM[3].

Author information

Abstract

Post-translational modification of proteins imparts diversity to protein functions. The process of glycation represents a complex set of pathways that mediates advanced glycation endproduct (AGE) formation, detoxification, intracellular disposition, extracellular release, and induction of signal transduction. These processes modulate the response to hyperglycemia, obesity, aging, inflammation, and renal failure, in which AGE formation and accumulation is facilitated. It has been shown that endogenous anti-AGE protective mechanisms are thwarted in chronic disease, thereby amplifying accumulation and detrimental cellular actions of these species. Atop these considerations, receptor for advanced glycation endproducts (RAGE)-mediated pathways downregulate expression and activity of the key anti-AGE detoxification enzyme, glyoxalase-1 (GLO1), thereby setting in motion an interminable feed-forward loop in which AGE-mediated cellular perturbation is not readily extinguished. In this review, we consider recent work in the field highlighting roles for glycation in obesity and atherosclerosis and discuss emerging strategies to block the adverse consequences of AGEs. This article is part of a Special Issue entitled: The role of post-translational protein modifications on heart and vascular metabolism edited by Jason R.B. Dyck & Jan F.C. Glatz.

Mol Cell Endocrinol. 2016 May 10. pii: S0303-7207(16)30157-5. doi: 10.1016/j.mce.2016.05.008. [Epub ahead of print]

Update on FGF23 and Klotho signaling.

Erben RG[1].

Author information

Abstract

Fibroblast growth factor-23 (FGF23) is a bone-derived hormone known to suppress phosphate reabsorption and vitamin D hormone production in the kidney. Klotho was originally discovered as an anti-aging factor, but the functional role of Klotho is still a controversial issue. Three major functions have been proposed, a hormonal function of soluble Klotho, an enzymatic function as glycosidase, and the function as an obligatory co-receptor for FGF23 signaling. The purpose of this review is to highlight the recent advances in the area of FGF23 and Klotho signaling in the kidney, in the parathyroid gland, in the cardiovascular system, in bone, and in the central nervous system. During recent years, major new functions of FGF23 and Klotho have been discovered in these organ systems. Based on these novel findings, FGF23 has emerged as a pleiotropic endocrine and auto-/paracrine factor influencing not only mineral metabolism but also cardiovascular function.

OTHER RESEARCH

Heales
HEALTHY LIFE EXTENSION SOCIETY

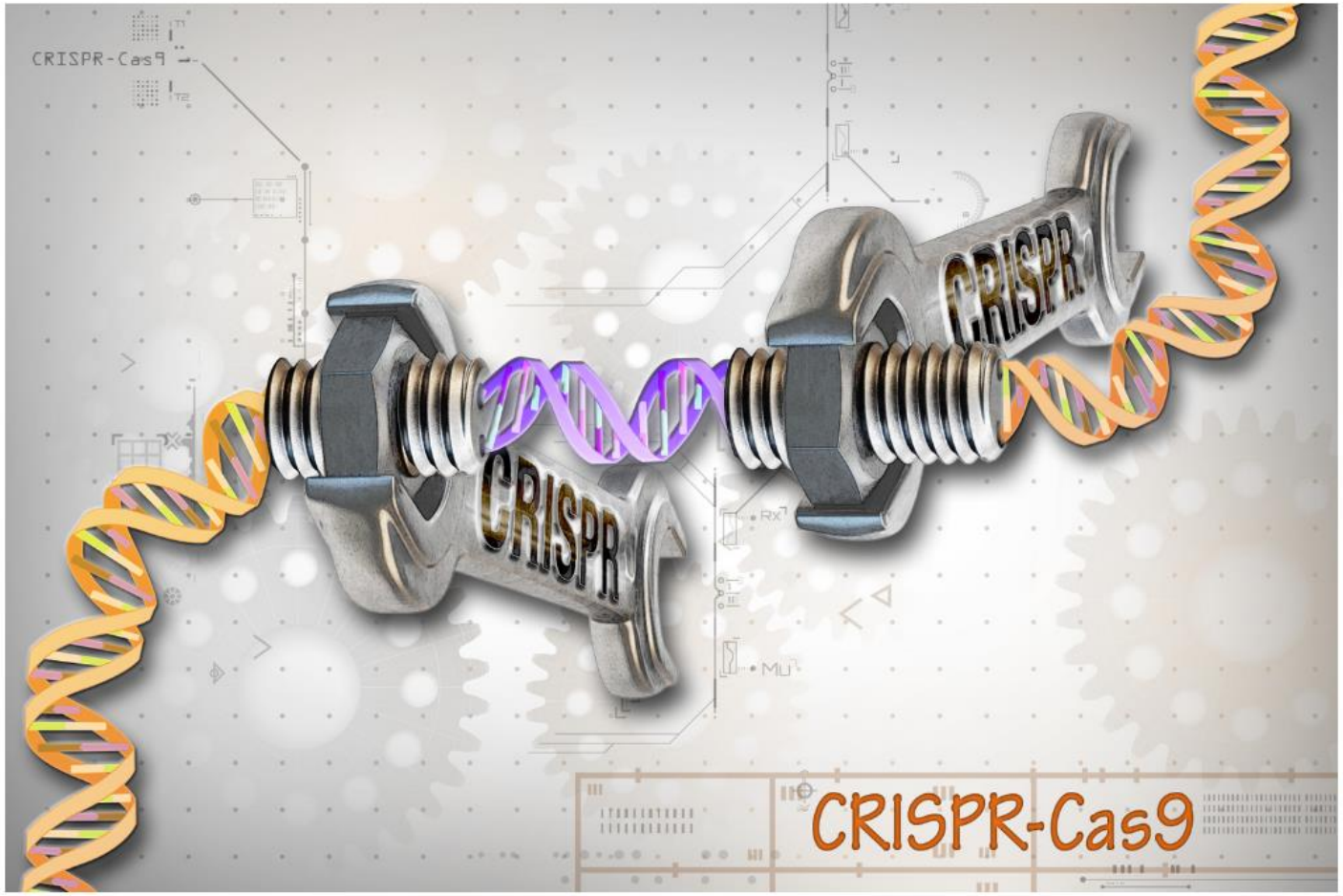
A Global Social Media Survey of Attitudes to Human Genome Editing

Tristan McCaughey[9], Paul G. Sanfilippo[9], George E.C. Gooden[9], David M. Budden[9], Li Fan, Eva Fenwick, Gwyneth Rees, Casimir MacGregor, Lei Si, Christine Chen, Helena Hai Liang, Timothy Baldwin, Alice Pébay[10], Alex W. Hewitt[10],

Ongoing breakthroughs with CRISPR/Cas-based editing could potentially revolutionize modern medicine, but there are many questions to resolve about the ethical implications for its therapeutic application. We conducted a worldwide online survey of over 12,000 people recruited via social media to gauge attitudes toward this technology and discuss our findings here.

Heales
HEALTHY LIFE EXTENSION SOCIETY

New Poll Investigates People's Opinion On Genome Editing



E. coli bacteria growing in a dish. VeeDunn/Flickr (CC BY 2.0)

Not unexpectedly, a new drug-resistant 'superbug' pops up in the United States

By Kelly Servick | May. 27. 2016 . 12:30 PM

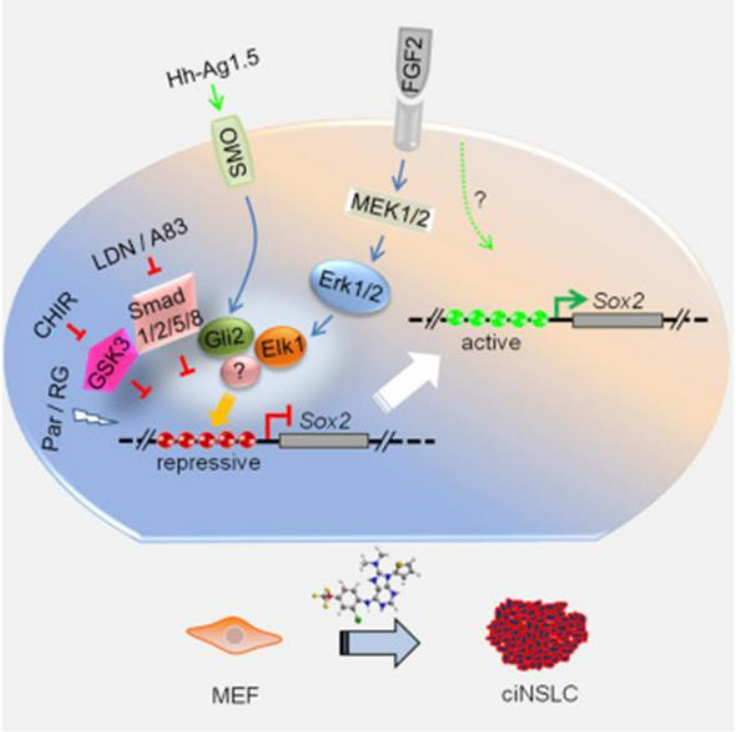
Pharmacological Reprogramming of Fibroblasts into Neural Stem Cells by Signaling-Directed Transcriptional Activation

Mingliang Zhang, Yuan-Hung Lin, Yujiao Jennifer Sun, Saiyong Zhu[10], Jiashun Zheng, Kai Liu, Nan Cao, Ke Li, Yadong Huang, Sheng Ding

Highlights

- Combinatorial screening identified a nine-component neural reprogramming cocktail
- Induced neural stem cell-like cells are tripotent in vitro and in vivo
- Gene expression analysis revealed specific activation of the neural program
- Transcriptional activation downstream of signaling drives the reprogramming process

Graphical Abstract



Summary

Cellular reprogramming using chemically defined conditions, without genetic manipulation, is a promising approach for generating clinically relevant cell types for regenerative medicine and drug discovery. However, small-molecule approaches for inducing lineage-specific stem cells from somatic cells across lineage boundaries have been challenging. Here, we report highly efficient reprogramming of mouse fibroblasts into induced neural stem cell-like cells (ciNSLCs) using a cocktail of nine components (M9). The resulting ciNSLCs closely resemble primary neural stem cells molecularly and functionally. Transcriptome analysis revealed that M9 induces a gradual and specific conversion of fibroblasts toward a neural fate. During reprogramming specific transcription factors such as Elk1 and Gli2 that are downstream of M9-induced signaling pathways bind and activate endogenous master neural genes to specify neural identity. Our study provides an effective chemical approach for generating neural stem cells from mouse fibroblasts and reveals mechanistic insights into underlying reprogramming processes.

Heales
HEALTHY LIFE EXTENSION SOCIETY

REPORT

Conversion of human fibroblasts into functional cardiomyocytes by small molecules

Nan Cao[1,2], Yu Huang[1], Jiashun Zheng[4,5], C. Ian Spencer[1], Yu Zhang[1,2], Ji-Dong Fu[6], Baoming Nie[1,2], Min Xie[1,2], Mingliang Zhang[1,2], Haixia Wang[1,2], Tianhua Ma[1,2], Tao Xu[1,2], Guilai Shi[1,2], Deepak Srivastava[1,3,4,*], Sheng Ding[1,2,*,†]

Reprogramming somatic fibroblasts into alternative lineages would provide a promising source of cells for regenerative therapy. However, transdifferentiating human cells into specific homogeneous, functional cell types is challenging. Here we show that cardiomyocyte-like cells can be generated by treating human fibroblasts with a combination of nine compounds that we term 9C. The chemically induced cardiomyocyte-like cells uniformly contracted and resembled human cardiomyocytes in their transcriptome, epigenetic, and electrophysiological properties. 9C treatment of human fibroblasts resulted in a more open-chromatin conformation at key heart developmental genes, enabling their promoters and enhancers to bind effectors of major cardiogenic signals. When transplanted into infarcted mouse hearts, 9C-treated fibroblasts were efficiently converted to chemically induced cardiomyocyte-like cells. This pharmacological approach to lineage-specific reprogramming may have many important therapeutic implications after further optimization to generate mature cardiac cells.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Science

PERSPECTIVES

Cite as: J. D. Boeke *et al.*, *Science* 10.1126/science.aaf6850 (2016).

The Genome Project-Write

Jef D. Boeke,*† George Church, * Andrew Hessel, * Nancy J. Kelley,* Adam Arkin, Yizhi Cai, Rob Carlson, Aravinda Chakravarti, Virginia W. Cornish, Liam Holt, Farren J. Isaacs, Todd Kuiken, Marc Lajoie, Tracy Lessor, Jeantine Lunshof, Matthew T. Maurano, Leslie A. Mitchell, Jasper Rine, Susan Rosser, Neville E. Sanjana, Pamela A. Silver, David Valle, Harris Wang, Jeffrey C. Way, Luhan Yang

*These authors contributed equally to this work.

†Corresponding author. Email: jef.boeke@nyumc.org

The list of author affiliations is available in the supplementary materials.

We need technology and an ethical framework for genome-scale engineering