Heales
HEALTHY LIFE EXTENSION SOCIETY

Scientific News
3rd of February 2019
Sven Bulterijs

Heales
HEALTHY LIFE EXTENSION SOCIETY

Heales
HEALTHY LIFE EXTENSION SOCIETY

JUVENESCENCE

Juvenescence is a bio-pharma development company which develops therapies that will allow people worldwide to live longer, healthier lives.

Juvenescence is the most prominent name in longevity biotechnology hosting a range of businesses

I would like to congratulate our investors, friends, business partners, and fellow longevity biotechnology experts at Juvenescence on the first close of their series B. The company now raised over $100 million and turned into a household name in the longevity biotechnology community. Everyone aspires to work with Juvenescence and develop life-saving products together.

UNITY Biotechnology Expands Ongoing UBX0101 Phase 1 Study to Further Evaluate SASP Factors in Osteoarthritis of the Knee

Unity Biotechnology, Inc. January 22, 2019

- Results expected in the second quarter of 2019 -

SAN FRANCISCO, Jan. 22, 2019 (GLOBE NEWSWIRE) -- UNITY Biotechnology, Inc. (UNITY) [NASDAQ:UBX], a biotechnology company developing therapeutics to extend healthspan by slowing, halting or reversing diseases of aging, today announced further expansion of the Phase 1 study of UBX0101 in patients with moderate to severe osteoarthritis (OA) of the knee with a cohort of an additional 24 patients at the highest evaluated dose (4mg) (Part B). Part B is intended to supplement the initial Phase 1 trial (Part A) by further evaluating the impact of UBX0101 on specific pro-inflammatory and extracellular matrix modifying factors within the Senescence-Associated Secretory Phenotype (SASP).

Heales
HEALTHY LIFE EXTENSION SOCIETY

Insilico and Elevian enter a research collaboration to discover drugs that target aging

Two longevity biotechnology companies partner to discover drugs that target aging

INSILICO MEDICINE, INC.

SHARE PRINT E-MAIL

Jan. 9, 2019, San Francisco, CA - On the final day of the largest biotechnology and pharmaceutical partnering week at the Juvenescence Longevity Showcase two leading longevity biotechnology companies, Elevian and Insilico Medicine announced a research and development partnership to develop oral medications targeting the GDF11 pathway and associated targets. Elevian is an emerging biotech company developing medicines that restore youthful regenerative capacity, with the potential to treat and prevent the diseases of aging. Its first target is the GDF11 pathway. Insilico Medicine is an Artificial Intelligence (AI) company developing an end-to-end pipeline for automated target identification, small molecule generation, prediction of clinical trials outcomes and aging research. It is a leader in the fields of deep learning for drug discovery, biomarker development, and anti-aging interventions. The collaboration will take advantage of Insilico's generative adversarial networks (GANs) and reinforcement learning (RL) AI technologies to discover novel small molecules that target the GDF11 pathway, which has been demonstrated to play an important role in aging and age-related disease.

IMAGE: INSILICO AND ELEVIAN ENTER A RESEARCH COLLABORATION TO DISCOVER DRUGS THAT TARGET AGING. view more ›

CREDIT: INSILICO MEDICINE

Heales
HEALTHY LIFE EXTENSION SOCIETY

AGEX THERAPEUTICS

ABOUT US LEADERSHIP TECHNOLOGY PIPELINE

09 Jan AgeX Therapeutics Publishes Data In Peer-Reviewed Journal To Advance Potential Cell Therapy AgeX-BAT1 For Type II Diabetes And Obesity

Posted at 07:50h in News by agexinc

- 30M U.S. adults suffer from diabetes and 93M from obesity, with associated medical costs of over $300B annually, necessitating an urgent need for novel treatments
- AgeX-BAT1 for Type II diabetes and obesity aims to return brown adipose tissue, also known as "brown" or "good" fat, back to levels found in young adults
- Loss of brown fat as a result of aging is associated with obesity and Type II diabetes as well as heightened cardiovascular risk
- Published data shows that AgeX's pioneering PureStem® cell therapy manufacturing platform generated highly pure, identifiable and scalable brown adipose cells, expressing active adipokines such as adiponectin

ALAMEDA, Calif. – January 9, 2019 – AgeX Therapeutics, Inc. (NYSE American: AGE) announced today the publication of data relating to its cell therapy product candidate AgeX-BAT1 for Type II diabetes and obesity in the peer-reviewed scientific journal Stem Cell Research & Therapy. Scientists now realize that the activity of brown adipose tissue (BAT), also known as "brown" or "good" fat, is markedly lost with age. This loss may contribute to metabolic disturbances seen in Type II diabetes and obesity as well as a heightened cardiovascular risk. AgeX-BAT1 is comprised of regenerative cells capable of becoming BAT and is intended to return BAT levels back to those found in young adults. AgeX is targeting Type II diabetes and obesity as they are areas of high unmet medical need and present multi-billion-dollar market opportunities.

As described in the paper, "Clonal Derivation of White and Brown Adipocyte Progenitor Cell Lines from Human Pluripotent Stem Cells," two AgeX-BAT1 cell lines, designated NP88 and NP110, were selected for detailed characterization. The data demonstrate AgeX's PureStem® cell therapy manufacturing platform was successful in generating highly purified cells with precise anatomical identity, and most importantly, capable of potently expressing definitive markers of BAT cells, including active adipokines such as adiponectin. Adiponectin is reported to have beneficial effects in patients with age-related metabolic and cardiovascular diseases. In addition, the paper provides evidence that AgeX's PureStem® technology allows for the reliable re-derivation of scalable lots of desired cells.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Genomics of 1 million parent lifespans implicates novel pathways and common diseases and distinguishes survival chances

We use a genome-wide association of 1 million parental lifespans of genotyped subjects and data on mortality risk factors to validate previously unreplicated findings near *CDKN2B-AS1*, *ATXN2/BRAP*, *FURIN/FES*, *ZW10*, *PSORS1C3*, and 13q21.31, and identify and replicate novel findings near *ABO*, *ZC3HC1*, and *IGF2R*. We also validate previous findings near 5q33.3/*EBF1* and *FOXO3*, whilst finding contradictory evidence at other loci. Gene set and cell-specific analyses show that expression in foetal brain cells and adult dorsolateral prefrontal cortex is enriched for lifespan variation, as are gene pathways involving lipid proteins and homeostasis, vesicle-mediated transport, and synaptic function. Individual genetic variants that increase dementia, cardiovascular disease, and lung cancer – but not other cancers – explain the most variance. Resulting polygenic scores show a mean lifespan difference of around five years of life across the deciles.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Identification of 12 genetic loci associated with human healthspan

Aging populations face diminishing quality of life due to increased disease and morbidity. These challenges call for longevity research to focus on understanding the pathways controlling healthspan. We use the data from the UK Biobank (UKB) cohort and observe that the risks of major chronic diseases increased exponentially and double every eight years, i.e., at a rate compatible with the Gompertz mortality law. Assuming that aging drives the acceleration in morbidity rates, we build a risk model to predict the age at the end of healthspan depending on age, gender, and genetic background. Using the sub-population of 300,447 British individuals as a discovery cohort, we identify 12 loci associated with healthspan at the whole-genome significance level. We find strong genetic correlations between healthspan and all-cause mortality, life-history, and lifestyle traits. We thereby conclude that the healthspan offers a promising new way to interrogate the genetics of human longevity.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Longevity defined as top 10% survivors and beyond is transmitted as a quantitative genetic trait

Survival to extreme ages clusters within families. However, identifying genetic loci conferring longevity and low morbidity in such longevous families is challenging. There is debate concerning the survival percentile that best isolates the genetic component in longevity. Here, we use three-generational mortality data from two large datasets, UPDB (US) and LINKS (Netherlands). We study 20,360 unselected families containing index persons, their parents, siblings, spouses, and children, comprising 314,819 individuals. Our analyses provide strong evidence that longevity is transmitted as a quantitative genetic trait among survivors up to the top 10% of their birth cohort. We subsequently show a survival advantage, mounting to 31%, for individuals with top 10% surviving first and second-degree relatives in both databases and across generations, even in the presence of non-longevous parents. To guide future genetic studies, we suggest to base case selection on top 10% survivors of their birth cohort with equally long-lived family members.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Naked mole-rat mortality rates defy Gompertzian laws by not increasing with age

The longest-lived rodent, the naked mole-rat (*Heterocephalus glaber*), has a reported maximum lifespan of >30 years and exhibits delayed and/or attenuated age-associated physiological declines. We questioned whether these mouse-sized, eusocial rodents conform to Gompertzian mortality laws by experiencing an exponentially increasing risk of death as they get older. We compiled and analyzed a large compendium of historical naked mole-rat lifespan data with >3000 data points. Kaplan-Meier analyses revealed a substantial portion of the population to have survived at 30 years of age. Moreover, unlike all other mammals studied to date, and regardless of sex or breeding-status, the age-specific hazard of mortality did not increase with age, even at ages 25-fold past their time to reproductive maturity. This absence of hazard increase with age, in defiance of Gompertz's law, uniquely identifies the naked mole-rat as a non-aging mammal, confirming its status as an exceptional model for biogerontology.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Cells exhibiting strong $p16^{INK4a}$ promoter activation in vivo display features of senescence

The activation of cellular senescence throughout the lifespan promotes tumor suppression, whereas the persistence of senescent cells contributes to aspects of aging. This theory has been limited, however, by an inability to identify and isolate individual senescent cells within an intact organism. Toward that end, we generated a murine reporter strain by "knocking-in" a fluorochrome, tandem-dimer Tomato (tdTom), into exon 1α of the $p16^{INK4a}$ locus. We used this allele ($p16^{tdTom}$) for the enumeration, isolation, and characterization of individual $p16^{INK4a}$-expressing cells ($tdTom^+$). The half-life of the knocked-in transcript was shorter than that of the endogenous $p16^{INK4a}$ mRNA, and therefore reporter expression better correlated with $p16^{INK4a}$ promoter activation than $p16^{INK4a}$ transcript abundance. The frequency of $tdTom^+$ cells increased with serial passage in cultured murine embryo fibroblasts from $p16^{tdTom/+}$ mice. In adult mice, $tdTom^+$ cells could be readily detected at low frequency in many tissues, and the frequency of these cells increased with aging. Using an in vivo model of peritoneal inflammation, we compared the phenotype of cells with or without activation of $p16^{INK4a}$ and found that $tdTom^+$ macrophages exhibited some features of senescence, including reduced proliferation, senescence-associated β-galactosidase (SA-β-gal) activation, and increased mRNA expression of a subset of transcripts encoding factors involved in SA-secretory phenotype (SASP). These results indicate that cells harboring activation of the $p16^{INK4a}$ promoter accumulate with aging and inflammation in vivo, and display characteristics of senescence.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Senolytics in idiopathic pulmonary fibrosis: Results from a first-in-human, open-label, pilot study

Background

Cellular senescence is a key mechanism that drives age-related diseases, but has yet to be targeted therapeutically in humans. Idiopathic pulmonary fibrosis (IPF) is a progressive, fatal cellular senescence-associated disease. Selectively ablating senescent cells using dasatinib plus quercetin (DQ) alleviates IPF-related dysfunction in bleomycin-administered mice.

Methods

A two-center, open-label study of intermittent DQ (D:100 mg/day, Q:1250 mg/day, three-days/week over three-weeks) was conducted in participants with IPF ($n=14$) to evaluate feasibility of implementing a senolytic intervention. The primary endpoints were retention rates and completion rates for planned clinical assessments. Secondary endpoints were safety and change in functional and reported health measures. Associations with the senescence-associated secretory phenotype (SASP) were explored.

Findings

Fourteen patients with stable IPF were recruited. The retention rate was 100% with no DQ discontinuation; planned clinical assessments were complete in 13/14 participants. One serious adverse event was reported. Non-serious events were primarily mild-moderate, with respiratory symptoms ($n=16$ total events), skin irritation/bruising (n=14), and gastrointestinal discomfort ($n=12$) being most frequent. Physical function evaluated as 6-min walk distance, 4-m gait speed, and chair-stands time was significantly and clinically-meaningfully improved ($p<.05$). Pulmonary function, clinical chemistries, frailty index (FI-LAB), and reported health were unchanged. DQ effects on circulat.ing SASP factors were inconclusive, but correlations were observed between change in function and change in SASP-related matrix-remodeling proteins, microRNAs, and pro-inflammatory cytokines (23/48 markers $r \geq 0.50$).

Interpretation

Our first-in-humans open-label pilot supports study feasibility and provides initial evidence that senolytics may alleviate physical dysfunction in IPF, warranting evaluation of DQ in larger randomized controlled trials for senescence-related diseases.

Heales
HEALTHY LIFE EXTENSION SOCIETY

New drugs for pharmacological extension of replicative life span in normal and progeroid cells

A high-throughput anti-aging drug screen was developed that simultaneously measures senescence-associated β-galactosidase activity and proliferation. Applied to replicatively pre-aged fibroblasts, this screen yielded violuric acid (VA) and 1-naphthoquinone-2-monoxime (N2N1) as its top two hits. These lead compounds extended the replicative life spans of normal and progeroid human cells in a dose-dependent manner and also extended the chronological life spans of mice and C. elegans. They are further shown here to function as redox catalysts in oxidations of NAD(P)H. They thus slow age-related declines in $NAD(P)^+$/NAD(P)H ratios. VA participates in non-enzymatic electron transfers from NAD(P)H to oxidized glutathione or peroxides. N2N1 transfers electrons from NAD(P)H to cytochrome c or CoQ_{10} via NAD(P)H dehydrogenase (quinone) 1 (NQO1). Our results indicate that pharmacologic manipulation of NQO1 activity via redox catalysts may reveal mechanisms of senescence and aging.

Using the drug-protein interactome to identify anti-ageing compounds for humans

Matías Fuentealba, Handan Melike Dönertaş, Rhianna Williams, Johnathan Labbadia, Janet M. Thornton, Linda Partridge

Advancing age is the dominant risk factor for most of the major killer diseases in developed countries. Hence, ameliorating the effects of ageing may prevent multiple diseases simultaneously. Drugs licensed for human use against specific diseases have proved to be effective in extending lifespan and healthspan in animal models, suggesting that there is scope for drug repurposing in humans. New bioinformatic methods to identify and prioritise potential anti-ageing compounds for humans are therefore of interest. In this study, we first used drug-protein interaction information, to rank 1,147 drugs by their likelihood of targeting ageing-related gene products in humans. Among 19 statistically significant drugs, 6 have already been shown to have pro-longevity properties in animal models ($p < 0.001$). Using the targets of each drug, we established their association with ageing at multiple levels of biological action including pathways, functions and protein interactions. Finally, combining all the data, we calculated a ranked list of drugs that identified tanespimycin, an inhibitor of HSP-90, as the top-ranked novel anti-ageing candidate. We experimentally validated the pro-longevity effect of tanespimycin through its HSP-90 target in *Caenorhabditis elegans*.

Genetic and pharmacological interventions in the aging motor nervous system slow motor aging and extend life span in *C. elegans*

As animals and humans age, the motor system undergoes a progressive functional decline, leading to frailty. Age-dependent functional deteriorations at neuromuscular junctions (NMJs) contribute to this motor aging. However, it is unclear whether one can intervene in this process to slow motor aging. The *Caenorhabditis elegans* BK channel SLO-1 dampens synaptic transmission at NMJs by repressing synaptic release from motor neurons. Here, we show that genetic ablation of SLO-1 not only reduces the rate of age-dependent motor activity decline to slow motor aging but also surprisingly extends life span. SLO-1 acts in motor neurons to mediate both functions. Genetic knockdown or pharmacological inhibition of SLO-1 in aged, but not young, worms can slow motor aging and prolong longevity. Our results demonstrate that genetic and pharmacological interventions in the aging motor nervous system can promote both health span and life span.

Porphyromonas gingivalis in Alzheimer's disease brains: Evidence for disease causation and treatment with small-molecule inhibitors

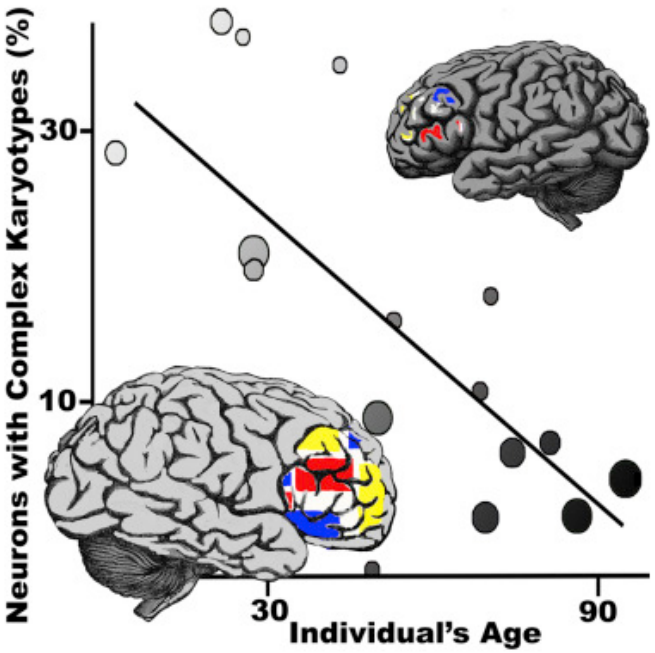
Abstract

Porphyromonas gingivalis, the keystone pathogen in chronic periodontitis, was identified in the brain of Alzheimer's disease patients. Toxic proteases from the bacterium called gingipains were also identified in the brain of Alzheimer's patients, and levels correlated with tau and ubiquitin pathology. Oral *P. gingivalis* infection in mice resulted in brain colonization and increased production of $A\beta_{1-42}$, a component of amyloid plaques. Further, gingipains were neurotoxic in vivo and in vitro, exerting detrimental effects on tau, a protein needed for normal neuronal function. To block this neurotoxicity, we designed and synthesized small-molecule inhibitors targeting gingipains. Gingipain inhibition reduced the bacterial load of an established *P. gingivalis* brain infection, blocked $A\beta_{1-42}$ production, reduced neuroinflammation, and rescued neurons in the hippocampus. These data suggest that gingipain inhibitors could be valuable for treating *P. gingivalis* brain colonization and neurodegeneration in Alzheimer's disease.

Neurons with Complex Karyotypes Are Rare in Aged Human Neocortex

A subset of human neocortical neurons harbors complex karyotypes wherein megabase-scale copy-number variants (CNVs) alter allelic diversity. Divergent levels of neurons with complex karyotypes (CNV neurons) are reported in different individuals, yet genome-wide and familial studies implicitly assume a single brain genome when assessing the genetic risk architecture of neurological disease. We assembled a brain CNV atlas using a robust computational approach applied to a new dataset (>800 neurons from 5 neurotypical individuals) and to published data from 10 additional neurotypical individuals. The atlas reveals that the frequency of neocortical neurons with complex karyotypes varies widely among individuals, but this variability is not readily accounted for by tissue quality or CNV detection approach. Rather, the age of the individual is anti-correlated with CNV neuron frequency. Fewer CNV neurons are observed in aged individuals than in young individuals.

Graphical Abstract



Heales
HEALTHY LIFE EXTENSION SOCIETY

Blood–brain barrier breakdown is an early biomarker of human cognitive dysfunction

Vascular contributions to cognitive impairment are increasingly recognized[1,2,3,4,5] as shown by neuropathological[6,7], neuroimaging[4,8,9,10,11], and cerebrospinal fluid biomarker[4,12] studies. Moreover, small vessel disease of the brain has been estimated to contribute to approximately 50% of all dementias worldwide, including those caused by Alzheimer's disease (AD)[3,4,13]. Vascular changes in AD have been typically attributed to the vasoactive and/or vasculotoxic effects of amyloid-β (Aβ)[3,11,14], and more recently tau[15]. Animal studies suggest that Aβ and tau lead to blood vessel abnormalities and blood–brain barrier (BBB) breakdown[14,15,16]. Although neurovascular dysfunction[3,11] and BBB breakdown develop early in AD[1,4,5,8,9,10,12,13], how they relate to changes in the AD classical biomarkers Aβ and tau, which also develop before dementia[17], remains unknown. To address this question, we studied brain capillary damage using a novel cerebrospinal fluid biomarker of BBB-associated capillary mural cell pericyte, soluble platelet-derived growth factor receptor-β[8,18], and regional BBB permeability using dynamic contrast-enhanced magnetic resonance imaging[8,9,10]. Our data show that individuals with early cognitive dysfunction develop brain capillary damage and BBB breakdown in the hippocampus irrespective of Alzheimer's Aβ and/or tau biomarker changes, suggesting that BBB breakdown is an early biomarker of human cognitive dysfunction independent of Aβ and tau.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Blood-brain barrier dysfunction in aging induces hyper-activation of TGF-beta signaling and chronic yet reversible neural dysfunction

Aging involves a decline in neural function that contributes to cognitive impairment and disease. However, the mechanisms underlying the transition from a young-and-healthy to aged-and-dysfunctional brain are not well understood. Here, we report breakdown of the vascular blood-brain barrier (BBB) in aging humans and rodents, which begins as early as middle age and progresses to the end of the lifespan. Gain-of-function and loss-of-function manipulations show that this BBB dysfunction triggers hyperactivation of transforming growth factor β (TGFβ) signaling in astrocytes, which is necessary and sufficient to cause neural dysfunction and age-related pathology. Specifically, infusion of the serum protein albumin into the young brain (mimicking BBB leakiness) induced astrocytic TGFβ signaling and an aged brain phenotype including aberrant electrocorticographic activity, vulnerability to seizures, and cognitive impairment. Furthermore, conditional genetic knockdown of astrocytic TGFβ receptors, or pharmacological inhibition of TGFβ signaling, reversed these symptomatic outcomes in aged mice. Finally, we found that this same signaling pathway is activated in aging human subjects with BBB dysfunction. Our study identifies dysfunction in the neurovascular unit as one of the earliest triggers of neurological aging, and demonstrates that the aging brain may retain considerable latent capacity which can be revitalized by therapeutic inhibition of TGFβ signaling.

Organoid-Induced Differentiation of Conventional T Cells from Human Pluripotent Stem Cells

The ability to generate T cells from pluripotent stem cells (PSCs) has the potential to transform autologous T cell immunotherapy by facilitating universal, off-the-shelf cell products. However, differentiation of human PSCs into mature, conventional T cells has been challenging with existing methods. We report that a continuous 3D organoid system induced an orderly sequence of commitment and differentiation from PSC-derived embryonic mesoderm through hematopoietic specification and efficient terminal differentiation to naive $CD3^+CD8\alpha\beta^+$ and $CD3^+CD4^+$ conventional T cells with a diverse T cell receptor (TCR) repertoire. Introduction of an MHC class I-restricted TCR in PSCs produced naive, antigen-specific $CD8\alpha\beta^+$ T cells that lacked endogenous TCR expression and showed anti-tumor efficacy *in vitro* and *in vivo*. Functional assays and RNA sequencing aligned PSC-derived T cells with primary naive $CD8^+$ T cells. The PSC-artificial thymic organoid (ATO) system presented here is an efficient platform for generating functional, mature T cells from human PSCs.

Centenarians Overexpress Pluripotency-Related Genes

Human mesenchymal cells can become pluripotent by the addition of Yamanaka factors *OCT3/4*, *SOX2*, *c-MYC*, *KLF4*. We have recently reported that centenarians overexpress *BCL-xL*, which has been shown to improve pluripotency; thus, we aimed to determine the expression of pluripotency-related genes in centenarians. We recruited 22 young, 32 octogenarian, and 47 centenarian individuals and determined the mRNA expression of Yamanaka factors and other stemness-related cell surface marker genes (*VIM*, *BMP4*, *NCAM*, *BMPR2*) in peripheral blood mononuclear cells by reverse transcription polymerase chain reaction. We found that centenarians overexpress *OCT3/4*, *SOX2*, *c-MYC*, *VIM*, *BMP4*, *NCAM*, and *BMPR2*, when compared with octogenarians ($p < .05$). We further tested the functional role of *BCL-xL* in centenarians' ability to express pluripotency-related genes: lymphocytes from octogenarians transduced with *BCL-xL* overexpressed *SOX2*, *c-MYC*, and *KLF4*. We conclude that centenarians overexpress Yamanaka Factors and other stemness-related cell surface marker genes, which may contribute to their successful aging.

Heales
HEALTHY LIFE EXTENSION SOCIETY

J Microbiol Biotechnol. 2019 Jan 11. doi: 10.4014/jmb.1811.11023. [Epub ahead of print]

Comparison of the Gut Microbiota of Centenarians in Longevity Villages of South Korea with Those of Other Age Groups.

Kim BS[1,2], Choi CW[3,4], Shin H[3,4], Jin SP[3,4,5], Bae JS[3,4,5], Han M[3,4,5], Seo EY[3,4], Chun J[6], Chung JH[3,4,5,7].

⊕ Author information

Abstract

Several studies have attempted to identify factors associated with longevity and maintenance of health in centenarians. In this study, we analyzed and compared the gut microbiota of centenarians in longevity villages with the elderly and adults in the same region and urbanized towns. Fecal samples were collected from centenarians, elderly, and young adults in longevity villages, and the gut microbiota sequences of elderly and young adults in urbanized towns of Korea were obtained from public databases. The relative abundance of *Firmicutes* was found to be considerably higher in subjects from longevity villages than those from urbanized towns, whereas *Bacteroidetes* was lower. Age-related rearrangement of gut microbiota was observed in centenarians, such as reduced proportions of *Faecalibacterium* and *Prevotella*, and increased proportion of *Escherichia*, along with higher abundances of *Akkermansia, Clostridium, Collinsella*, and uncultured *Christensenellaceae*. Gut microbiota of centenarians in rehabilitation hospital were also different to those residing at home. These differences could be due to differences in diet patterns and living environments. In addition, phosphatidylinositol signaling system, glycosphingolipid biosynthesis, and various types of N-glycan biosynthesis were predicted to be higher in the gut microbiota of centenarians (corrected $p < 0.05$). These three metabolic pathways of gut microbiota can be associated with the immune status and healthy gut environment of centenarians. Although further studies are necessary to validate the function of microbiota between groups, this study provides valuable information on centenarians' gut microbiota.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Blood Biochemistry Analysis to Detect Smoking Status and Quantify Accelerated Aging in Smokers

There is an association between smoking and cancer, cardiovascular disease and all-cause mortality. However, currently, there are no affordable and informative tests for assessing the effects of smoking on the rate of biological aging. In this study we demonstrate for the first time that smoking status can be predicted using blood biochemistry and cell count results andthe recent advances in artificial intelligence (AI). By employing age-prediction models developed using supervised deep learning techniques, we found that smokers exhibited higher aging rates than nonsmokers, regardless of their cholesterol ratios and fasting glucose levels. We further used those models to quantify the acceleration of biological aging due to tobacco use. Female smokers were predicted to be twice as old as their chronological age compared to nonsmokers, whereas male smokers were predicted to be one and a half times as old as their chronological age compared to nonsmokers. Our findings suggest that deep learning analysis of routine blood tests could complement or even replace the current error-prone method of self-reporting of smoking status and could be expanded to assess the effect of other lifestyle and environmental factors on aging.

Diet-induced β-cell insulin resistance results in reversible loss of functional β-cell mass

ABSTRACT: Although convincing in genetic models, the relevance of β-cell insulin resistance in diet-induced type 2 diabetes (T2DM) remains unclear. Exemplified by diabetes-prone, male, C57B1/6J mice being fed different combinations of Western-style diet, we show that β-cell insulin resistance occurs early during T2DM progression and is due to a combination of lipotoxicity and increased β-cell workload. Within 8 wk of being fed a high-fat, high-sucrose diet, mice became obese, developed impaired insulin and glucose tolerances, and displayed noncompensatory insulin release, due, at least in part, to reduced expression of syntaxin-1A. Through reporter islets transplanted to the anterior chamber of the eye, we demonstrated a concomitant loss of functional β-cell mass. When mice were changed from diabetogenic diet to normal chow diet, the diabetes phenotype was reversed, suggesting a remarkable plasticity of functional β-cell mass in the early phase of T2DM development. Our data reinforce the relevance of diet composition as an environmental factor determining different routes of diabetes progression in a given genetic background. Employing the *in vivo* reporter islet–monitoring approach will allow researchers to define key times in the dynamics of reversible loss of functional β-cell mass and, thus, to investigate the underlying, molecular mechanisms involved in the progression toward T2DM manifestation.—Paschen, M., Moede, T., Valladolid-Acebes, I., Leibiger, B., Moruzzi, N., Jacob, S., García-Prieto, C. F., Brismar, K., Leibiger, I. B., Berggren, P.-O. Diet-induced β-cell insulin resistance results in reversible loss of functional β-cell mass. FASEB J. 33, 204–218 (2019). www.fasebj.org

Heales
HEALTHY LIFE EXTENSION SOCIETY

Young plasma attenuates age-dependent liver ischemia reperfusion injury

Anding Liu,* Jiankun Yang,* Qi Hu,† Olaf Dirsch,‡ Uta Dahmen,§ Cuntai Zhang,† David A. Gewirtz,¶ Haoshu Fang,‖ and Jian Sun#,**,1

ABSTRACT: Aging is often associated with a decreased autophagic activity that contributes to the high sensitivity of aged livers to ischemia reperfusion injury (IRI). Blood from young animals can positively affect aged animals. This study was designed to evaluate the effect of young plasma in a model of liver IRI in aged rats. Aged rats were treated with pooled plasma collected from young rats before ischemia. Administration of young plasma restored aging-induced suppression in hepatic autophagic activity and reduced liver IRI. Inhibition of the young-plasma–restored autophagic activity abrogated the beneficial effect of young plasma against liver IRI. Similarly, young serum restored autophagic activity and reduced cellular injury after hypoxia/reoxygenation (H/R) in primary old rat hepatocytes. Mechanistic studies showed thatadministration of young plasma increased AMPK phosphorylation and led to unc-51–like autophagy activating kinase (ULK)1 activation. Furthermore, AMPK-inhibition abrogated the young serum-induced ULK1 activation and autophagic activity and diminished the protective action of young serum against H/R injury in primary old rat hepatocytes, whereas AMPK-activation potentiated the effects of young serum. Young plasma could restore age-impaired autophagy, at least in part, *via* AMPK/ULK1 signaling. Restoration of age-impaired autophagic activity may be a critical contributing mechanism to young-plasma–afforded protection against liver IRI in aged rats.—Liu, A., Yang, J., Hu, Q., Dirsch, O., Dahmen, U., Zhang, C., Gewirtz, D. A., Fang, H., Sun, J. Young plasma attenuates age-dependent liver ischemia reperfusion injury. FASEB J. 33, 3063–3073 (2019). www.fasebj.org

Heales
HEALTHY LIFE EXTENSION SOCIETY

Behav Brain Res. 2019 Jan 28. pii: S0166-4328(18)31414-1. doi: 10.1016/j.bbr.2019.01.048. [Epub ahead of print]

Metformin administration prevents memory impairment induced by hypobaric hypoxia in rats.

Zhao M[1], Cheng X[1], Lin X[1], Han Y[1], Zhou Y[1], Zhao T[1], He Y[1], Wu L[1], Zhao Y[1], Fan M[2], Zhu L[3].

Author information

Abstract

Metformin, an antidiabetic biguanide, reduces hyperglycemia by improving glucose utilization and reducing gluconeogenesis. Recently, an increasing number of studies have shown that metformin also led to a significant clinical improvement in memory and cognition in different clinical settings. In the present study, we investigated whether metformin administration protects against memory impairment and neuron damage caused by acute exposure to hypobaric hypoxia and screened the possible molecular mechanisms with a focused gene array. We found that metformin treatment obviously attenuated spatial memory and recognition memory impairment resulting from acute hypobaric hypoxia exposure but had no effect on general locomotor and behavioral activity. Moreover, the results of Nissl and TUNEL staining showed that neuron damage and cell apoptosis caused by hypobaric hypoxia exposure was also inhibited by metformin pretreatment. At the molecular level, we found that metformin pretreatment not only prevented the changes of FOS, JUNB and BDNF at both mRNA and protein levels, but also increased the expression of the postsynaptic scaffold genes HOMER and PSD95 after exposure to hypobaric hypoxia. These data suggested that metformin pretreatment is a feasible strategy for preventing memory impairment under hypobaric hypoxia.

Cardiovasc Res. 2019 Jan 17. doi: 10.1093/cvr/cvz010. [Epub ahead of print]

ESC Working Group on Cellular Biology of the Heart: Tissue Engineering and Cell-Based Therapies for Cardiac Repair in Ischemic Heart Disease and Heart Failure.

Madonna R[1], Van Laake LW[2], Botker HE[3], Davidson SM[4], De Caterina R[1,5], Engel FB[6], Eschenhagen T[7], Fernandez-Aviles F[8], Hausenloy DJ[9], Hulot JS[10], Lecour S[11], Leor J[12], Menasché P[13], Pesce M[14], Perrino C[15], Prunier F[16], Van Linthout S[17], Ytrehus K[18], Zimmermann WH[19,20], Ferdinandy P[21], Sluijter JPG[22].

Author information

Abstract

Morbidity and mortality from ischemic heart disease (IHD) and heart failure (HF) remain significant in Europe and are increasing worldwide. Patients with IHD or HF might benefit from novel therapeutic strategies, such as cell-based therapies. We recently discussed the therapeutic potential of cell-based therapies and provided recommendations on how to improve the therapeutic translation of these novel strategies for effective cardiac regeneration and repair. Despite major advances in optimizing these strategies with respect to cell source and delivery method, the clinical outcome of cell-based therapy remains unsatisfactory. Major obstacles are the low engraftment and survival rate of transplanted cells in the harmful microenvironment of the host tissue, and the paucity or even lack of endogenous cells with repair capacity. Therefore, new ways of delivering cells and their derivatives are required in order to empower cell-based cardiac repair and regeneration in patients with IHD or HF. Strategies using tissue engineering (TE) combine cells with matrix materials to enhance cell retention or cell delivery in the transplanted area, and have recently received much attention for this purpose. Here, we summarize knowledge on novel approaches emerging from the TE scenario. In particular, we will discuss how combinations of cell/bio-materials (e.g., hydrogels, cell sheets, prefabricated matrices, microspheres, and injectable matrices) combinations might enhance cell retention or cell delivery in the transplantation areas and thereby increase the success rate of cell therapies for IHD and HF. We will not focus on the use of classical engineering approaches, employing fully synthetic materials, because of their unsatisfactory material properties which render them not clinically applicable. The overall aim of this Position Paper from the ESC Working Group Cellular Biology of the Heart is to provide recommendations on how to proceed in research with these novel tissue engineering strategies combined with cell-based therapies to boost cardiac repair in the clinical settings of IHD and HF.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Association of All-Cause and Cardiovascular Mortality With High Levels of Physical Activity and Concurrent Coronary Artery Calcification

Design, Setting, and Participants The Cooper Center Longitudinal Study is a prospective observational study of patients from the Cooper Clinic, a preventive medicine facility. The present study included participants seen from January 13, 1998, through December 30, 2013, with mortality follow-up through December 31, 2014. A total of 21758 generally healthy men without prevalent cardiovascular disease (CVD) were included if they reported their physical activity level and underwent CAC scanning. Data were analyzed from September 26, 2017, through May 2, 2018.

Exposures Self-reported physical activity was categorized into at least 3000 (n=1561), 1500 to 2999 (n=3750), and less than 1500 (n=16 447) metabolic equivalent of task (MET)-minutes/week (min/wk). The CAC scores were categorized into at least 100 (n=5314) and less than 100 (n=16 444) Agatston units (AU).

Main Outcomes and Measures All-cause and CVD mortality collected from the National Death Index Plus.

Results Among the 21 758 male participants, baseline mean (SD) age was 51.7 (8.4) years. Men with at least 3000 MET-min/wk were more likely to have prevalent CAC of at least 100 AU (relative risk, 1.11; 95% CI, 1.03-1.20) compared with those accumulating less physical activity. In the group with physical activity of at least 3000 MET-min/wk and CAC of at least 100 AU, mean (SD) CAC level was 807 (1120) AU. After a mean (SD) follow-up of 10.4 (4.3) years, 759 all-cause and 180 CVD deaths occurred, including 40 all-cause and 10 CVD deaths among those with physical activity of at least 3000 MET-min/wk. Men with CAC of less than 100 AU and physical activity of at least 3000 MET-min/wk were about half as likely to die compared with men with less than 1500 MET-min/wk (hazard ratio [HR], 0.52; 95% CI, 0.29-0.91). In the group with CAC of at least 100 AU, men with at least 3000 MET-min/wk did not have a significant increase in all-cause mortality (HR, 0.77; 95% CI, 0.52-1.15) when compared with men with physical activity of less than 1500 MET-min/wk. In the least active men, those with CAC of at least 100 AU were twice as likely to die of CVD compared with those with CAC of less than 100 AU (HR, 1.93; 95% CI, 1.34-2.78).

Conclusions and Relevance This study suggests there is evidence that high levels of physical activity (≥3000 MET-min/wk) are associated with prevalent CAC but are not associated with increased all-cause or CVD mortality after a decade of follow-up, even in the presence of clinically significant CAC levels.

The individual's signature of telomere length distribution

Mean telomere length in human leukocyte DNA samples reflects the different lengths of telomeres at the ends of the 23 chromosomes and in an admixture of cells. However, only rudimentary information is available regarding the distribution of telomere lengths in all chromosomes and the different cell types in leukocyte samples. Understanding the configuration of leukocyte telomere length distribution (LTLD) could be helpful in capturing intrinsic elements that are not provided by the mean leukocyte telomere length (mLTL). The objective of this study was to analyse LTLD and its temporal variation in adults. Leukocyte samples were donated on two occasions (8 years apart) by 72 participants in the ADELAHYDE study. Telomere length was measured by Southern blotting of the terminal restriction fragments. Individuals with comparable mLTLs displayed different shapes of LTLDs. Inter-individual variation in LTLD shape was much larger than intra-individual variation in LTLD shape between baseline and follow-up leukocyte samples. These results show an important individual stability of LTLD shape over time indicating that each individual has a characteristic LTLD signature.

Mathematical model and computer simulations of telomere loss

Ana Martinčić Špoljarić [1, 2, a] ✉, Ivica Rubelj [b] ✉, Miljenko Huzak [c] ✉

The molecular mechanisms that control the limited number of human cell divisions has occupied researchers ever since its first description in 1961. There is evidence that this limited growth capacity, referred to as cellular or replicative senescence, is the basis for organismal ageing. Numerous studies point to the molecular mechanisms of telomere involvement in this phenomenon. A hallmark of cell senescence is high stochasticity where individual cells enter senescence in a completely random and stochastic fashion. Therefore, mathematical modelling and computational simulations of telomere dynamics are often used to explain this stochastic nature of cell ageing. Models published thus far were based on the molecular mechanisms of telomere biology and how they dictate the dynamics of cell culture proliferation. In the present work we propose an advanced model of telomere controlled cell senescence based on abrupt telomere shortening, thus explaining some important but thus far overlooked aspects of cell senescence. We test our theory by simulating the proliferative potential and two-sister experiment originally conducted by Smith and Whitney in 1980.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Mech Ageing Dev. 2019 Jan 16;178:64-71. doi: 10.1016/j.mad.2019.01.006. [Epub ahead of print]

Glycation interferes with natural killer cell function.

Rosenstock P[1], Bezold V[2], Bork K[2], Scheffler J[2], Horstkorte R[2].

⊕ Author information

Abstract

One hallmark of molecular aging is glycation, better known as formation of so-called advanced glycation end products (AGEs), where reactive carbonyls react with amino-groups of proteins. AGEs accumulate over time and are responsible for various age-dependent diseases and impairments. Two very potent dicarbonyls to generate AGEs are glyoxal (GO) and methylglyoxal (MGO). The plasma level of such dicarbonyls is higher in aging and age-related diseases. Natural killer (NK) cells are cells of the innate immune system and provide a major defense against tumor cells and virus infected cells. They are able to kill modified or infected cells and produce different cytokines to modulate the function of other immune cells. Here we investigated the effect of GO- and MGO-induced glycation on the function of NK cells. Using the human NK cell line NK-92, we could demonstrate that both GO and MGO lead to glycation of cellular proteins, but that MGO interferes much stronger with NK cell function (cytotoxicity) than GO. In addition, glycation of NK cell targets, such as K562 tumor cells, also interferes with their lysis by NK cells. From this data we conclude that glycation acts negatively on NK cells function and reduces their cytotoxic potential towards tumor cells.

Arthritis Res Ther. 2019 Jan 11;21(1):18. doi: 10.1186/s13075-018-1801-y.

Impairment of glyoxalase-1, an advanced glycation end-product detoxifying enzyme, induced by inflammation in age-related osteoarthritis.

Trellu S[1,2,3,4], Courties A[1,2,3,4], Jaisson S[5], Gorisse L[5], Gillery P[5], Kerdine-Römer S[6], Vaamonde-Garcia C[1,2,3,7], Houard X[1,2,3], Ekhirch FP[8], Sautet A[1,9], Friguet B[1,10], Jacques C[1,2,3], Berenbaum F[11,12,13,14], Sellam J[1,2,3,4].

⊕ Author information

Abstract

BACKGROUND: Accumulation of advanced glycation end-products (AGEs) is involved in age-related osteoarthritis (OA). Glyoxalase (Glo)-1 is the main enzyme involved in the removal of AGE precursors, especially carboxymethyl-lysine (CML). We aimed to investigate the expression of several AGEs and Glo-1 in human OA cartilage and to study chondrocytic Glo-1 regulation by inflammation, mediated by interleukin (IL)-1β.

METHODS: Ex vivo, we quantified AGEs (pentosidine, CML, methylglyoxal-hydroimidazolone-1) in knee cartilage from 30 OA patients. Explants were also incubated with and without IL-1β, and we assessed Glo-1 protein expression and enzymatic activity. In vitro, primary cultured murine chondrocytes were stimulated with increasing concentrations of IL-1β to assess Glo-1 enzymatic activity and expression. To investigate the role of oxidative stress in the IL-1β effect, cells were also treated with inhibitors of mitochondrial oxidative stress or nitric oxide synthase.

RESULTS: Ex vivo, only the human cartilage CML content was correlated with patient age ($r = 0.78$, $p = 0.0031$). No statistically significant correlation was found between Glo-1 protein expression and enzymatic activity in human cartilage and patient age. We observed that cartilage explant stimulation with IL-1β decreased Glo-1 protein expression and enzymatic activity. In vitro, we observed a dose-dependent decrease in Glo-1 mRNA, protein quantity, and enzymatic activity in response to IL-1β in murine chondrocytes. Inhibitors of oxidative stress blunted this downregulation.

CONCLUSION: Glo-1 is impaired by inflammation mediated by IL-1β in chondrocytes through oxidative stress pathways and may explain age-dependent accumulation of the AGE CML in OA cartilage.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Clin Immunol. 2019 Jan 16;200:24-30. doi: 10.1016/j.clim.2019.01.005. [Epub ahead of print]

Dissecting alterations in human CD8+ T cells with aging by high-dimensional single cell mass cytometry.

Shin MS[1], Yim K[2], Moon K[2], Park HJ[1], Mohanty S[1], Kim JW[1], Montgomery RR[1], Shaw AC[1], Krishnaswamy S[2], Kang I[3].

Author information

Abstract

We investigated the effect of aging on the multi-dimensional characteristics and heterogeneity of human peripheral $CD8^+$ T cells defined by the expression of a set of molecules at the single cell level using the recently developed mass cytometry or Cytometry by Time-Of-Flight (CyTOF) and computational algorithms. $CD8^+$ T cells of young and older adults had differential expression of molecules, especially those related to cell activation and migration, permitting the clustering of young and older adults through an unbiased approach. The changes in the expression of individual molecules were collectively reflected in the altered high-dimensional profiles of $CD8^+$ T cells in older adults as visualized by the dimensionality reduction analysis tools principal component analysis (PCA) and t-distributed stochastic neighbor embedding (t-SNE). A combination of PhenoGraph clustering and t-SNE analysis revealed heterogeneous subsets of $CD8^+$ T cells that altered with aging. Furthermore, intermolecular quantitative relationships in $CD8^+$ T cells appeared to change with age as determined by the computational algorithm conditional-Density Resampled Estimate of Mutual Information (DREMI). The results of our study showed that heterogeneity, multidimensional characteristics, and intermolecular quantitative relationships in human $CD8^+$ T cells altered with age, distinctively clustering young and older adults through an unbiased approach.

Aging (Albany NY). 2019 Jan 23;11(2):590-614. doi: 10.18632/aging.101762.

Relationship between senescence in macaques and bone marrow mesenchymal stem cells and the molecular mechanism.

Pan XH[1,2,3], Chen YH[1,2,3], Yang YK[1,2,3], Zhang XJ[1,2,3], Lin QK[1,2,3], Li ZA[1,2,3], Cai XM[1,2,3], Pang RQ[1,2,3], Zhu XQ[1,2,3], Ruan GP[1,2,3].

Author information

Abstract

The relationship between bone marrow mesenchymal stem cells (BMSCs) and aging, as well as the antiaging effects of BMSCs, was observed. An aging macaque BMSC model was established. We isolated BMSCs from young and aged macaques and used RT-PCR and Western blot to confirm the aging-related mRNAs and their expression, revealing that TERT, SIRT1 and SIRT6 expression was decreased in the aged BMSCs. The morphology, immunophenotype, differentiation potential, proliferation potential, and antiaging effects of aged and young BMSCs on 293T cells were compared. The expression of aging-related genes and the difference between the secreted cytokines in natural aging and induced aging BMSCs were observed. The transcriptome of peripheral blood mononuclear cells from macaques was analyzed by high-throughput sequencing. Finally, the transcriptional characteristics and regulatory mechanisms of gene transcription in aging macaques were investigated.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Redox Biol. 2019 Jan 11;21:101108. doi: 10.1016/j.redox.2019.101108. [Epub ahead of print]

Non-enzymatic cleavage of Hsp90 by oxidative stress leads to actin aggregate formation: A novel gain-of-function mechanism.

Castro JP[1], Fernando R[2], Reeg S[2], Meinl W[2], Almeida H[3], Grune T[4].

Author information

Abstract

Aging is accompanied by the accumulation of oxidized proteins. To remove them, cells employ the proteasomal and autophagy-lysosomal systems; however, if the clearance rate is inferior to its formation, protein aggregates form as a hallmark of proteostasis loss. In cells, during stress conditions, actin aggregates accumulate leading to impaired proliferation and reduced proteasomal activity, as observed in cellular senescence. The heat shock protein 90 (Hsp90) is a molecular chaperone that binds and protects the proteasome from oxidative inactivation. We hypothesized that in oxidative stress conditions a malfunction of Hsp90 occurs resulting in the aforementioned protein aggregates. Here, we demonstrate that upon oxidative stress Hsp90 loses its function in a highly specific non-enzymatic iron-catalyzed oxidation event and its breakdown product, a cleaved form of Hsp90 (Hsp90cl), acquires a new function in mediating the accumulation of actin aggregates. Moreover, the prevention of Hsp90 cleavage reduces oxidized actin accumulation, whereas transfection of the cleaved form of Hsp90 leads to an enhanced accumulation of oxidized actin. This indicates a clear role of the Hsp90cl in the aggregation of oxidized proteins.

Mech Ageing Dev. 2019 Jan 16. pii: S0047-6374(18)30176-3. doi: 10.1016/j.mad.2019.01.002. [Epub ahead of print]

Brain region-specific effects of long-term caloric restriction on redox balance of the aging rat.

Moyse E[1], Arsenault M[2], Gaudreau P[3], Ferland G[4], Ramassamy C[5].

Author information

Abstract

Caloric restriction (CR) is the most effective intervention to improve health span and extend lifespan in preclinical models. This anti-aging effect of CR is related to attenuation of oxidative damage in various tissues, with divergent results in the brain. We addressed how brain oxidoreductive balance would be modulated in male Sprague-Dawley (SD) rats submitted to a 40% CR from 8 to 19 months of age, by reference to ad libitum-fed (AL) rats at 2 and 19 months of age. Four brain structures were compared: hippocampus, striatum, parietal cortex, cerebellum. Our CR diet elicits significant prevention of oxidative damages with the upregulation of antioxidant defenses (levels of glutathione [GSH], mRNAs of clusterin and of three key antioxidant enzymes) as compared to age-matched AL controls, in a strikingly region-specific pattern. CR also prevented a drastic rise of the glial fibrillary acidic protein in the hippocampus of old AL rats. Besides, the CR effects at age 19 months mainly consist in improving endogenous defenses before the onset of age-related redox alterations. These effects are more prominent in the hippocampus.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Lysosomal Signaling Promotes Longevity by Adjusting Mitochondrial Activity

Prasanna V. Ramachandran [1, 2, 4, 6], Marzia Savini [3, 6], Andrew K. Folick [3, 4, 6], Kuang Hu [2], Ruchi Masand [1], Brett H. Graham [1, 7], Meng C. Wang [1, 2, 5, 8]

Lysosomes and mitochondria are both crucial cellular organelles for metabolic homeostasis and organism health. However, mechanisms linking their metabolic activities to promote organism longevity remain poorly understood. We discovered that the induction of specific lysosomal signaling mediated by a LIPL-4 lysosomal acid lipase and its lipid chaperone LBP-8 increases mitochondrial ß-oxidation to reduce lipid storage and promote longevity in *Caenorhabditis elegans*. We further discovered that increased mitochondrial ß-oxidation reduces mitochondrial electron transport chain complex II activity, contributing to the induction of reactive oxygen species in mitochondria (mtROS) and the longevity effect conferred by LIPL-4–LBP-8 signaling. Moreover, by activating the JUN-1 transcription factor downstream of mtROS, the LIPL-4–LBP-8 signaling pathway induces antioxidant targets and oxidative stress tolerance. Together, these results reveal regulatory mechanisms by which lysosomal signaling triggers adjustments in mitochondrial activity and suggest the significance of these metabolic adjustments for improving metabolic fitness, redox homeostasis, and longevity.

REVIEWS/COMMENTS/ METHODS/EDITORIALS

Heales
HEALTHY LIFE EXTENSION SOCIETY

Rapamycin and Alzheimer's disease: Time for a clinical trial?

Matt Kaeberlein[1,*] and Veronica Galvan[2,3,*]

Abstract

The drug rapamycin has beneficial effects in a number of animal models of neurodegeneration and aging including mouse models of Alzheimer's disease. Despite its compelling preclinical record, no clinical trials have tested rapamycin or other mTOR inhibitors in patients with Alzheimer's disease. We argue that such clinical trials should be undertaken.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Cellular Senescence: Aging, Cancer, and Injury

Arianna Calcinotto, Jaskaren Kohli, Elena Zagato, Laura Pellegrini, Marco Demaria, and Andrea Alimonti

16 JAN 2019 // https://doi.org/10.1152/physrev.00020.2018

Cellular senescence is a permanent state of cell cycle arrest that occurs in proliferating cells subjected to different stresses. Senescence is, therefore, a cellular defense mechanism that prevents the cells to acquire an unnecessary damage. The senescent state is accompanied by a failure to re-enter the cell cycle in response to mitogenic stimuli, an enhanced secretory phenotype and resistance to cell death. Senescence takes place in several tissues during different physiological and pathological processes such as tissue remodeling, injury, cancer, and aging. Although senescence is one of the causative processes of aging and it is responsible of aging-related disorders, senescent cells can also play a positive role. In embryogenesis and tissue remodeling, senescent cells are required for the proper development of the embryo and tissue repair. In cancer, senescence works as a potent barrier to prevent tumorigenesis. Therefore, the identification and characterization of key features of senescence, the induction of senescence in cancer cells, or the elimination of senescent cells by pharmacological interventions in aging tissues is gaining consideration in several fields of research. Here, we describe the known key features of senescence, the cell-autonomous, and noncell-autonomous regulators of senescence, and we attempt to discuss the functional role of this fundamental process in different contexts in light of the development of novel therapeutic targets.

Rejuvenation Res. 2019 Jan 29. doi: 10.1089/rej.2017.2048. [Epub ahead of print]

Frailty and Rejuvenation with Stem Cells: Therapeutic Opportunities and Clinical Challenges.

Sun X[1], Hao Q[2], Tang R[3], Xiao C[4], Ge M[5], Dong B[6,7].

Author information

Abstract

Frailty, one appealing target for improving successful aging of the elderly population, is a common clinical syndrome based on the accumulation of multisystemic function declines and the increase in susceptibility to stressors during biological aging. The age-dependent senescence, the frailty-related stem cell depletion, chronic inflammation, imbalance of immune homeostasis, and the reduction of multipotent stem cells, collectively suggest the rational hypothesis that it is possible to (partially) cure frailty with stem cells. This systematic review has included all of the human trials of stem cell therapy for frailty from the main electronic databases and printed materials and screened the closely related reviews themed on the mechanisms of aging, frailty, and stem cells, to provide more insights in stem cell strategies for frailty, one promising method to recover health from a frail status. To date, a total of four trials about this subject have been registered on clinicaltrials.gov. The use of mesenchymal stem cells (MSCs), doses of 100 million cells, single peripheral intravenous infusion, follow-up periods of 6~12 months, and a focus primarily on safety and secondarily on efficacy are common characteristics of these studies. We conclude that intravenous infusion of allogenic MSCs is safe, well tolerated, and preliminarily effective clinically. More preclinical experiments and clinical trials are warranted to precisely elucidate the mechanism, safety, and efficacy of frailty stem cell therapy.

Turning fibroblasts into cardiomyocytes: technological review of cardiac transdifferentiation strategies

Kristin Klose, Manfred Gossen, and Christof Stamm

To date, no viable therapeutic options exist for the effective and sustained reversal of cardiac failure, other than heart transplantation and mechanical circulatory assist devices. Therefore, divergent strategies aiming at the *de novo* formation of contractile tissue, as a prerequisite for the restoration of cardiac pump function, are currently being pursued. Clinical trials involving the transplantation of somatic progenitor cells failed. The search for alternative cell-based strategies to combat the consequences of ischemic injury has sparked widespread interest in the genetic and pharmacologic reprogramming of fibroblasts into cardiomyocytes, harnessing the abundant *in vivo* pool of cardiac fibroblasts. Here, we provide a comprehensive overview of *in vitro* and *in vivo* cardiac reprogramming studies identified in an extensive literature search. We systematically review and evaluate feasibility, efficiency, and reproducibility of the different technologies currently being explored. Finally, we discuss potential safety issues deduced from preclinical studies and identify obstacles that must be overcome before clinical translation.—Klose, K., Gossen, M., Stamm, C. Turning fibroblasts into cardiomyocytes: technological review of cardiac transdifferentiation strategies.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Autophagy and cardiac aging

Shigeki Miyamoto

Cardiovascular disease (CVD) is the leading cause of death and the prevalence of CVD dramatically increases with age. Cardiac aging is associated with hypertrophy, fibrosis, inflammation, and decreased contractility. Autophagy, a bulk degradation/recycling system, is essential to maintain cellular homeostasis. Cardiac autophagy is decreased with age, and misfolded proteins and dysfunctional mitochondria are accumulated in the aging heart. Inhibition of autophagy leads to exacerbated cardiac aging, while stimulation of autophagy improves cardiac function and also increases lifespan in many organisms. Thus autophagy represents a potential therapeutic target for aging-related cardiac dysfunction. This review discusses recent progress in our understanding of the role and regulation of autophagy in the aging heart.

Mitochondrion. 2019 Jan 18. pii: S1567-7249(17)30317-3. doi: 10.1016/j.mito.2019.01.001. [Epub ahead of print]

The relevance of the supramolecular arrangements of the respiratory chain complexes in human diseases and aging.

Ramírez-Camacho I[1], Flores-Herrera O[2], Zazueta C[3].

Author information

Abstract

Mitochondrial dysfunction, a common factor in several diseases is accompanied with reactive oxygen species (ROS) production. These molecules react with proteins and lipids at their site of generation, establishing a vicious cycle which might result in further mitochondrial injury. It is well established that mitochondrial respiratory complexes can be organized into supramolecular structures called supercomplexes (SCs) or respirasomes; yet, the physiological/pathological relevance of these structures remains unresolved. Changes in their stabilization and content have been documented in Barth's syndrome, degenerative diseases such as Parkinson's and Alzheimer, cardiovascular diseases including heart failure and ischemia-reperfusion damage, as well as in aging. Under pathological conditions, SCs stability could have relevant biomedical implications or might be used as a reliable marker of mitochondrial damage. The purpose of this review is to recapitulate the current state of the significance on mitochondrial bioenergetics of these structures and their possible role in pathophysiologies related with ROS increase.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Treating osteoporosis to prevent fractures: current concepts and future developments

Mattias Lorentzon

Antiresorptive drugs, such as the bisphosphonates and the RANKL inhibitor denosumab, are currently the most widely used osteoporosis medications. These drugs increase bone mineral density (BMD) and reduce the risk of vertebral (by 40–70%), nonvertebral (by 25–40%) and hip fractures (by 40–53%) in postmenopausal women with osteoporosis. Due to the risk of rare side-effects, the use of bisphosphonates has been limited to up to 10 years with oral bisphosphonates and 6 years with intravenous zoledronic acid. Despite their well-proven efficacy and safety, few women at high risk of fracture are started on treatment. Case finding strategies, such as fracture risk-based screening in primary care using the fracture risk assessment tool (FRAX) and Fracture Liaison Services, have proved effective in increasing treatment rates and reducing fracture rates. Recently, anabolic therapy with teriparatide was demonstrated to be superior to the bisphosphonate risedronate in preventing vertebral and clinical fractures in postmenopausal women with vertebral fracture. Treatment with the sclerostin antibody romosozumab increases BMD more profoundly and rapidly than alendronate and is also superior to alendronate in reducing the risk of vertebral and nonvertebral fracture in postmenopausal women with osteoporosis. For patients with severe osteoporosis and high fracture risk, bisphosphonates alone are unlikely to be able to provide long-term protection against fracture and restore BMD. For those patients, sequential treatment, starting with a bone-building drug (e.g. teriparatide), followed by an antiresorptive, will likely provide better long-term fracture prevention and should be the golden standard of future osteoporosis treatment.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Artificial intelligence for aging and longevity research: Recent advances and perspectives

The applications of modern artificial intelligence (AI) algorithms within the field of aging research offer tremendous opportunities. Aging is an almost universal unifying feature possessed by all living organisms, tissues, and cells. Modern deep learning techniques used to develop age predictors offer new possibilities for formerly incompatible dynamic and static data types. AI biomarkers of aging enable a holistic view of biological processes and allow for novel methods for building causal models—extracting the most important features and identifying biological targets and mechanisms. Recent developments in generative adversarial networks (GANs) and reinforcement learning (RL) permit the generation of diverse synthetic molecular and patient data, identification of novel biological targets, and generation of novel molecular compounds with desired properties and geroprotectors. These novel techniques can be combined into a unified, seamless end-to-end biomarker development, target identification, drug discovery and real world evidence pipeline that may help accelerate and improve pharmaceutical research and development practices. Modern AI is therefore expected to contribute to the credibility and prominence of longevity biotechnology in the healthcare and pharmaceutical industry, and to the convergence of countless areas of research.

Heales
HEALTHY LIFE EXTENSION SOCIETY

The nematode *Caenorhabditis elegans* as a model for aging research

Hildegard I.D. Mack [1], Thomas Heimbucher [2], Coleen T. Murphy [2]

Show more

https://doi.org/10.1016/j.ddmod.2018.11.001

The nematode *Caenorhabditis elegans* is a key model system for experimental research on the genetic regulation of aging, and has paved the way towards many important discoveries in this field. Importantly, in the course of its short lifespan of ~3 weeks, *C. elegans* displays many phenotypic, behavioral, and molecular changes that are widely shared among metazoans as they age. In this review, we summarize how aging research takes advantage of *C. elegans*' biology, and we describe the experimental toolbox available to study worm aging.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Free Radic Biol Med. 2019 Jan 14. pii: S0891-5849(18)32591-7. doi: 10.1016/j.freeradbiomed.2019.01.016. [Epub ahead of print]

Redox regulation by NRF2 in aging and disease.

Schmidlin CJ[1], Dodson MB[1], Madhavan L[2], Zhang DD[3].

Author information

Abstract

NRF2, a transcription factor that has been deemed the master regulator of cellular redox homeostasis, declines with age. NRF2 transcriptionally upregulates genes that combat oxidative stress; therefore, loss of NRF2 allows oxidative stress to go unmitigated and drive the aging phenotype. Oxidative stress is a common theme among the key features associated with the aging process, collectively referred to as the "Hallmarks of Aging", as it disrupts proteostasis, alters genomic stability, and leads to cell death. In this review, we outline the role that oxidative stress and the reduction of NRF2 play in each of the Hallmarks of Aging, including how they contribute to the onset of neurodegenerative disorders, cancer, and other age-related pathologies.

OTHER RESEARCH

Heales
HEALTHY LIFE EXTENSION SOCIETY

News Feature: What are the limits of deep learning?

M. Mitchell Waldrop

PNAS January 22, 2019 116 (4) 1074-1077; https://doi.org/10.1073/pnas.1821594116

Article | Figures & SI | Info & Metrics | PDF

The much-ballyhooed artificial intelligence approach boasts impressive feats but still falls short of human brainpower. Researchers are determined to figure out what's missing.

There's no mistaking the image: It's a banana—a big, ripe, bright-yellow banana. Yet the artificial intelligence (AI) identifies it as a toaster, even though it was trained with the same powerful and oft-publicized deep-learning techniques that have produced a white-hot revolution in driverless cars, speech understanding, and a multitude of other AI applications. That means the AI was shown several thousand photos of bananas, slugs, snails, and similar-looking objects, like so many flash cards, and then drilled on the answers until it had the classification down cold. And yet this advanced system was quite easily confused—all it took was a little day-glow sticker, digitally pasted in one corner of the image.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Extreme opponents of genetically modified foods know the least but think they know the most

Philip M. Fernbach ✉, Nicholas Light, Sydney E. Scott, Yoel Inbar & Paul Rozin

There is widespread agreement among scientists that genetically modified foods are safe to consume[1,2] and have the potential to provide substantial benefits to humankind[3]. However, many people still harbour concerns about them or oppose their use[4,5]. In a nationally representative sample of US adults, we find that as extremity of opposition to and concern about genetically modified foods increases, objective knowledge about science and genetics decreases, but perceived understanding of genetically modified foods increases. Extreme opponents know the least, but think they know the most. Moreover, the relationship between self-assessed and objective knowledge shifts from positive to negative at high levels of opposition. Similar results were obtained in a parallel study with representative samples from the United States, France and Germany, and in a study testing attitudes about a medical application of genetic engineering technology (gene therapy). This pattern did not emerge, however, for attitudes and beliefs about climate change.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Gene annotation errors are common in the mammalian mitochondrial genomes database

Results

Using a combination of bioinformatics methods to carefully examine the mitochondrial gene arrangements in 304 mammalian species, we determined that there are only two sets of gene arrangements, one that is shared by all of the marsupials and another that is shared by all of the monotremes and eutherians, with these two arrangements differing only by the positions of tRNA genes in the region commonly designated as "WANCY" for the genes it comprises. All of the 68 other cases of reported gene rearrangements are errors. We note that there are also numerous errors of impossibly short, incorrect gene annotations, cases where genomes that are reported as complete are actually missing portions of the sequence, and genes that are clearly present but were not annotated in these records.

Conclusions

We judge that the application of simple bioinformatic tools in the verification of gene annotation, particularly for organelle genomes, would be a very useful enhancement for the curation of genome sequences submitted to GenBank.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Improving the metabolic fidelity of cancer models with a physiological cell culture medium

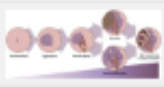
Abstract

Currently available cell culture media may not reproduce the in vivo metabolic environment of tumors. To demonstrate this, we compared the effects of a new physiological medium, Plasmax, with commercial media. We prove that the disproportionate nutrient composition of commercial media imposes metabolic artifacts on cancer cells. Their supraphysiological concentrations of pyruvate stabilize hypoxia-inducible factor 1α in normoxia, thereby inducing a pseudohypoxic transcriptional program. In addition, their arginine concentrations reverse the urea cycle reaction catalyzed by argininosuccinate lyase, an effect not observed in vivo, and prevented by Plasmax in vitro. The capacity of cancer cells to form colonies in commercial media was impaired by lipid peroxidation and ferroptosis and was rescued by selenium present in Plasmax. Last, an untargeted metabolic comparison revealed that breast cancer spheroids grown in Plasmax approximate the metabolic profile of mammary tumors better. In conclusion, a physiological medium improves the metabolic fidelity and biological relevance of in vitro cancer models.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Cell Stem Cell

Special Issue: Stem Cell Mechanisms of Cancer



Cancer Stem Cells: The Architects of the Tumor Ecosystem

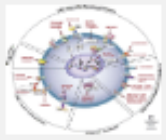
Briana C. Prager, Qi Xie, Shideng Bao, Jeremy N. Rich
Published in issue: January 03, 2019

Constructing and Deconstructing Cancers using Human Pluripotent Stem Cells and Organoids

Ryan C. Smith, Viviane Tabar
Published online: December 20, 2018

Cellular Plasticity in Intestinal Homeostasis and Disease

Felipe de Sousa e Melo, Frederic J. de Sauvage
Published online: December 27, 2018



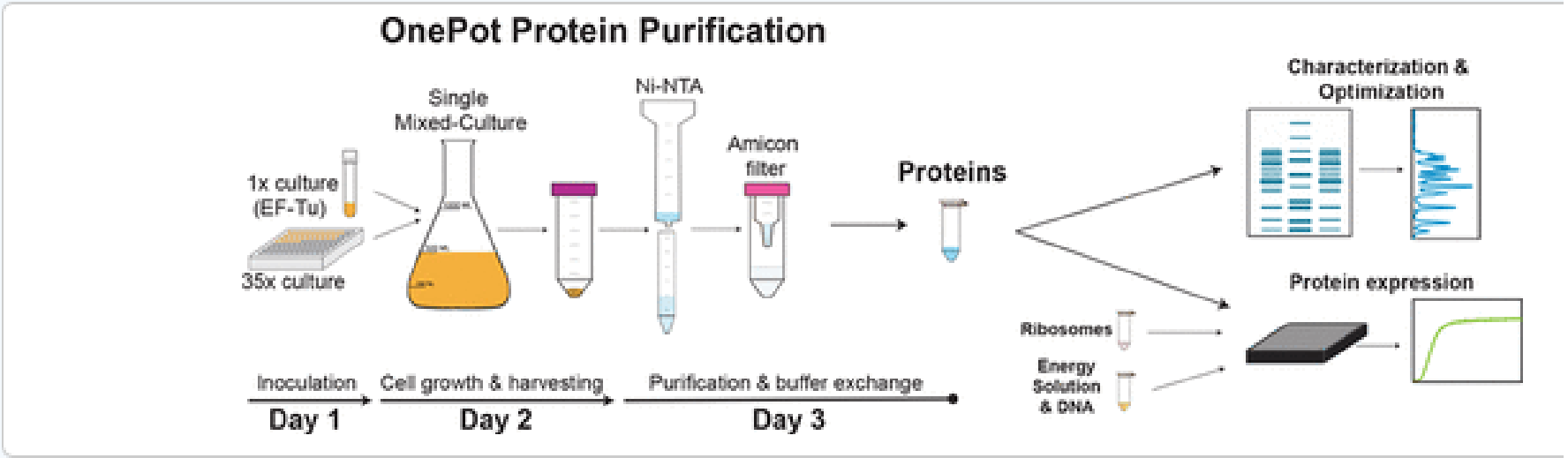
Targeting Cancer Stemness in the Clinic: From Hype to Hope

Caner Saygin, Daniela Matei, Ravindra Majeti, Ofer Reizes, Justin D. Lathia
Published online: December 27, 2018

Phenotypic Plasticity: Driver of Cancer Initiation, Progression, and Therapy Resistance

Piyush B. Gupta, Ievgenia Pastushenko, Adam Skibinski, Cedric Blanpain, Charlotte Kuperwasser
Published online: December 13, 2018

A Simple, Robust, and Low-Cost Method To Produce the PURE Cell-Free System



We demonstrate a simple, robust, and low-cost method for producing the PURE cell-free transcription–translation system. Our OnePot PURE system achieved a protein synthesis yield of 156 μg/mL at a cost of 0.09 USD/μL, leading to a 14-fold improvement in cost normalized protein synthesis yield over existing PURE systems. The one-pot method makes the PURE system easy to generate and allows it to be readily optimized and modified.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Identification of preexisting adaptive immunity to Cas9 proteins in humans

The CRISPR–Cas9 system is a powerful tool for genome editing, which allows the precise modification of specific DNA sequences. Many efforts are underway to use the CRISPR–Cas9 system to therapeutically correct human genetic diseases[1,2,3,4,5,6]. The most widely used orthologs of Cas9 are derived from *Staphylococcus aureus* and *Streptococcus pyogenes*[5,7]. Given that these two bacterial species infect the human population at high frequencies[8,9], we hypothesized that humans may harbor preexisting adaptive immune responses to the Cas9 orthologs derived from these bacterial species, SaCas9 (*S. aureus*) and SpCas9 (*S. pyogenes*). By probing human serum for the presence of anti-Cas9 antibodies using an enzyme-linked immunosorbent assay, we detected antibodies against both SaCas9 and SpCas9 in 78% and 58% of donors, respectively. We also found anti-SaCas9 T cells in 78% and anti-SpCas9 T cells in 67% of donors, which demonstrates a high prevalence of antigen-specific T cells against both orthologs. We confirmed that these T cells were Cas9-specific by demonstrating a Cas9-specific cytokine response following isolation, expansion, and antigen restimulation. Together, these data demonstrate that there are preexisting humoral and cell-mediated adaptive immune responses to Cas9 in humans, a finding that should be taken into account as the CRISPR–Cas9 system moves toward clinical trials.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Allele-specific RNA imaging shows that allelic imbalances can arise in tissues through transcriptional bursting

Orsolya Symmons, Marcello Chang, Ian A. Mellis, Jennifer M. Kalish, Jihwan Park, Katalin Suszták, Marisa S. Bartolomei, Arjun Raj

Extensive cell-to-cell variation exists even among putatively identical cells, and there is great interest in understanding how the properties of transcription relate to this heterogeneity. Differential expression from the two gene copies in diploid cells could potentially contribute, yet our ability to measure from which gene copy individual RNAs originated remains limited, particularly in the context of tissues. Here, we demonstrate quantitative, single molecule allele-specific RNA FISH adapted for use on tissue sections, allowing us to determine the chromosome of origin of individual RNA molecules in formaldehyde-fixed tissues. We used this method to visualize the allele-specific expression of *Xist* and multiple autosomal genes in mouse kidney. By combining these data with mathematical modeling, we evaluated models for allele-specific heterogeneity, in particular demonstrating that apparent expression from only one of the alleles in single cells can arise as a consequence of low-level mRNA abundance and transcriptional bursting.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Universal scaling across biochemical networks on Earth

Hyunju Kim[1,2,*], Harrison B. Smith[2,*], Cole Mathis[1,3], Jason Raymond[2] and Sara I. Walker[1,2,4,5,†]

Abstract

The application of network science to biology has advanced our understanding of the metabolism of individual organisms and the organization of ecosystems but has scarcely been applied to life at a planetary scale. To characterize planetary-scale biochemistry, we constructed biochemical networks using a global database of 28,146 annotated genomes and metagenomes and 8658 cataloged biochemical reactions. We uncover scaling laws governing biochemical diversity and network structure shared across levels of organization from individuals to ecosystems, to the biosphere as a whole. Comparing real biochemical reaction networks to random reaction networks reveals that the observed biological scaling is not a product of chemistry alone but instead emerges due to the particular structure of selected reactions commonly participating in living processes. We show that the topology of biochemical networks for the three domains of life is quantitatively distinguishable, with >80% accuracy in predicting evolutionary domain based on biochemical network size and average topology. Together, our results point to a deeper level of organization in biochemical networks than what has been understood so far.

Heales
HEALTHY LIFE EXTENSION SOCIETY

Extensive Unexplored Human Microbiome Diversity Revealed by Over 150,000 Genomes from Metagenomes Spanning Age, Geography, and Lifestyle

The body-wide human microbiome plays a role in health, but its full diversity remains uncharacterized, particularly outside of the gut and in international populations. We leveraged 9,428 metagenomes to reconstruct 154,723 microbial genomes (45% of high quality) spanning body sites, ages, countries, and lifestyles. We recapitulated 4,930 species-level genome bins (SGBs), 77% without genomes in public repositories (unknown SGBs [uSGBs]). uSGBs are prevalent (in 93% of well-assembled samples), expand underrepresented phyla, and are enriched in non-Westernized populations (40% of the total SGBs). We annotated 2.85 M genes in SGBs, many associated with conditions including infant development (94,000) or Westernization (106,000). SGBs and uSGBs permit deeper microbiome analyses and increase the average mappability of metagenomic reads from 67.76% to 87.51% in the gut (median 94.26%) and 65.14% to 82.34% in the mouth. We thus identify thousands of microbial genomes from yet-to-be-named species, expand the pangenomes of human-associated microbes, and allow better exploitation of metagenomic technologies.

Heales
HEALTHY LIFE EXTENSION SOCIETY

The importance of synthetic chemistry in the pharmaceutical industry

Kevin R. Campos[1,*], Paul J. Coleman[1,*], Juan C. Alvarez[1], Spencer D. Dreher[1], Robert M. Garbaccio[1], Nicholas K. Terrett[1], R...

Abstract

Innovations in synthetic chemistry have enabled the discovery of many breakthrough therapies that have improved human health over the past century. In the face of increasing challenges in the pharmaceutical sector, continued innovation in chemistry is required to drive the discovery of the next wave of medicines. Novel synthetic methods not only unlock access to previously unattainable chemical matter, but also inspire new concepts as to how we design and build chemical matter. We identify some of the most important recent advances in synthetic chemistry as well as opportunities at the interface with partner disciplines that are poised to transform the practice of drug discovery and development.