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Scientific News
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Sven Bulterijs

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DrugAge: Database of Ageing-Related Drugs

at the Human Ageing Genomic Resources

Build 1 (24/02/2016): 1,133 entries

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DrugAge Database of Anti-Ageing Drugs

The DrugAge database contains an extensive compilation of drugs, compounds and supplements (including natural products and nutraceuticals) with anti-ageing properties that extend longevity in model organisms. Our focus is on drugs/compounds potentially impacting on ageing, and therefore drugs/compounds extending lifespan in disease-prone animals (e.g., cancer models) are excluded.

Browse & Search

Search DrugAge for any term (case insensitive) or browse all the data.

Search

Drug Search

Retrieve specific drug data from DrugAge.

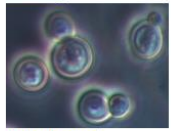
Search Drugs

Search Organism

Mouse

Fruit fly

Roundworm



Baker's yeast

Acheta domesticus | Search Organism

Highly Charged Proteins: The Achilles' Heel of Aging Proteomes

Adam M.R. de Graff, Michael J. Hazoglou, Ken A. Dill

Highlights

- Proteins undergo random damage from oxidation in aging
- Oxidative damage can change side chain charge, leading to protein stability loss
- Highly charged proteins are at particular risk of large oxidative stability loss
- Key pathways and aggregates of old cells are enriched in highly charged proteins

Summary

As cells and organisms age, their proteins sustain increasing amounts of oxidative damage. It is estimated that half of all proteins are damaged in old organisms, yet the dominant mechanisms by which damage affects proteins and cellular phenotypes are not known. Here, we show that random modification of side chain charge induced by oxidative damage is likely to be a dominant source of protein stability loss in aging cells. Using an established model of protein electrostatics, we find that short, highly charged proteins are particularly susceptible to large destabilization from even a single side chain oxidation event. This mechanism identifies 20 proteins previously established to be important in aging that are at particularly high risk for oxidative destabilization, including transcription factors, histone and histone-modifying proteins, ribosomal and telomeric proteins, and proteins essential for homeostasis. Cellular processes enriched in high-risk proteins are shown to be particularly abundant in the aggregates of old organisms.

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Could Oxidative Damage To Proteins Be Involved In Aging?

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

Xiyan Li & Michael P Snyder

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.

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Telomerase gene therapy rescues telomere length, bone marrow aplasia and survival in mice with aplastic anemia

Christian Bär[1], Juan Manuel Povedano[1], Rosa Serrano[1], Carlos Benitez-Buelga[2], Miriam Popkes[1], Ivan Formentini[3], Maria Bobadilla[4], Fatima Bosch[5], and Maria A. Blasco[6],*

Aplastic anemia is a fatal bone marrow disorder characterized by peripheral pancytopenia and marrow hypoplasia. The disease can be hereditary or acquired and develops at any stage of life. A subgroup of the inherited form is caused by replicative impairment of hematopoietic stem and progenitor cells owing to very short telomeres due to mutations in telomerase and other telomere components. Abnormal telomere shortening is also described in cases of acquired aplastic anemia, most likely secondary to increased turnover of bone marrow stem and progenitor cells. Here, we test the therapeutic efficacy of telomerase activation by using AAV9 gene therapy vectors carrying the telomerase *Tert* gene in two independent mouse models of aplastic anemia owing to short telomeres (*Trf1* and *Tert*-deficient mice). We find that a high dose of AAV9-*Tert* targets the bone marrow compartment including hematopoietic stem cells. AAV9-*Tert* treatment following telomere attrition in bone marrow cells rescues aplastic anemia and mouse survival compared with mice treated with the empty vector (AAV9-empty). Improved survival is associated with a significant increase in telomere length in peripheral blood and bone marrow cells as well as improved blood counts. These findings indicate that telomerase gene therapy represents a novel therapeutic strategy to treat aplastic anemia provoked or associated with short telomeres.

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Determinants of rodent longevity in the chaperone-protein degradation network

Karl A. Rodriguez, Joseph M. Valentine, David A. Kramer, Jonathan A. Gelfond, Deborah M. Kristan, Eviatar Nevo, Rochelle Buffenstein

Abstract

Proteostasis is an integral component of healthy aging, ensuring maintenance of protein structural and functional integrity with concomitant impact upon health span and longevity. In most metazoans, increasing age is accompanied by a decline in protein quality control resulting in the accrual of damaged, self-aggregating cytotoxic proteins. A notable exception to this trend is observed in the longest-lived rodent, the naked mole-rat (*NMR*, *Heterocephalus glaber*) which maintains proteostasis and proteasome-mediated degradation and autophagy during aging. We hypothesized that high levels of the proteolytic degradation may enable better maintenance of proteostasis during aging contributing to enhanced species maximum lifespan potential (MLSP). We test this by examining proteasome activity, proteasome-related HSPs, the heat-shock factor 1 (HSF1) transcription factor, and several markers of autophagy in the liver and quadriceps muscles of eight rodent species with divergent MLSP. All subterranean-dwelling species had higher levels of proteasome activity and autophagy, possibly linked to having to dig in soils rich in heavy metals and where underground atmospheres have reduced oxygen availability. Even after correcting for phylogenetic relatedness, a significant ($p < 0.02$) positive correlation between MLSP, HSP25, HSF1, proteasome activity, and autophagy-related protein 12 (ATG12) was observed, suggesting that the proteolytic degradation machinery and maintenance of protein quality play a pivotal role in species longevity among rodents.

Kinetic model of the aggregation of alpha-synuclein provides insights into prion-like spreading

The protein alpha-synuclein (αS) self-assembles into small oligomeric species and subsequently into amyloid fibrils that accumulate and proliferate during the development of Parkinson's disease. However, the quantitative characterization of the aggregation and spreading of αS remains challenging to achieve. Previously, we identified a conformational conversion step leading from the initially formed oligomers to more compact oligomers preceding fibril formation. Here, by a combination of single-molecule fluorescence measurements and kinetic analysis, we find that the reaction in solution involves two unimolecular structural conversion steps, from the disordered to more compact oligomers and then to fibrils, which can elongate by further monomer addition. We have obtained individual rate constants for these key microscopic steps by applying a global kinetic analysis to both the decrease in the concentration of monomeric protein molecules and the increase in oligomer concentrations over a 0.5–140-μM range of αS. The resulting explicit kinetic model of αS aggregation has been used to quantitatively explore seeding the reaction by either the compact oligomers or fibrils. Our predictions reveal that, although fibrils are more effective at seeding than oligomers, very high numbers of seeds of either type, of the order of 10^4, are required to achieve efficient seeding and bypass the slow generation of aggregates through primary nucleation. Complementary cellular experiments demonstrated that two orders of magnitude lower numbers of oligomers were sufficient to generate high levels of reactive oxygen species, suggesting that effective templated seeding is likely to require both the presence of template aggregates and conditions of cellular stress.

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Anti-myostatin antibody increases muscle mass and strength and improves insulin sensitivity in old mice

Sarcopenia, or skeletal muscle atrophy, is a debilitating comorbidity of many physiological and pathophysiological processes, including normal aging. There are no approved therapies for sarcopenia, but the antihypertrophic myokine myostatin is a potential therapeutic target. Here, we show that treatment of young and old mice with an anti-myostatin antibody (ATA 842) for 4 wk increased muscle mass and muscle strength in both groups. Furthermore, ATA 842 treatment also increased insulin-stimulated whole body glucose metabolism in old mice, which could be attributed to increased insulin-stimulated skeletal muscle glucose uptake as measured by a hyperinsulinemic-euglycemic clamp. Taken together, these studies provide support for pharmacological inhibition of myostatin as a potential therapeutic approach for age-related sarcopenia and metabolic disease.

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C. elegans lifespan extension by osmotic stress requires FUdR, base excision repair, FOXO, and sirtuins

Edward N. Anderson[a, 1], Mark E. Corkins[a, 2], Jia-Cheng Li[a], Komudi Singh[a, 3], Sadé Parsons[a], Tim M. Tucey[a, 4], Altar Sorkaç[a], Huiyan Huang[a], Maria Dimitriadi[a, 5], David A. Sinclair[b], Anne C. Hart[a]

Abstract

Moderate stress can increase lifespan by hormesis, a beneficial low-level induction of stress response pathways. 5′-fluorodeoxyuridine (FUdR) is commonly used to sterilize *Caenorhabditis elegans* in aging experiments. However, FUdR alters lifespan in some genotypes and induces resistance to thermal and proteotoxic stress. We report that hypertonic stress in combination with FUdR treatment or inhibition of the FUdR target thymidylate synthase, TYMS-1, extends *C. elegans* lifespan by up to 30%. By contrast, in the absence of FUdR, hypertonic stress decreases lifespan. Adaptation to hypertonic stress requires diminished Notch signaling and loss of Notch co-ligands leads to lifespan extension only in combination with FUdR. Either FUdR treatment or TYMS-1 loss induced resistance to acute hypertonic stress, anoxia, and thermal stress. FUdR treatment increased expression of DAF-16 FOXO and the osmolyte biosynthesis enzyme GPDH-1. FUdR-induced hypertonic stress resistance was partially dependent on sirtuins and base excision repair (BER) pathways, while FUdR-induced lifespan extension under hypertonic stress conditions requires DAF-16, BER, and sirtuin function. Combined, these results demonstrate that FUdR, through inhibition of TYMS-1, activates stress response pathways in somatic tissues to confer hormetic resistance to acute and chronic stress. *C. elegans* lifespan studies using FUdR may need re-interpretation in light of this work.

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Oncotarget. 2016 Feb 26. doi: 10.18632/oncotarget.7759. [Epub ahead of print]

Aging is a weak but relentless determinant of dementia severity.

Royall DR[1,2,3,4], Palmer RF[3].

Author information

Abstract

Structural Equation Models (SEM) can explicitly distinguish "dementia-relevant" variance in cognitive task performance (i.e., "δ" for dementia). In prior work, δ appears to uniquely account for dementia severity regardless of the cognitive measures used to construct it. In this study, we test δ as a mediator of age's prospective association with future cognitive performance and dementia severity in a large, ethnically diverse longitudinal cohort, the Texas Alzheimer's Research and Care Consortium (TARCC). Age had adverse effects on future cognition, and these were largely mediated through δ, independently of education, ethnicity, gender, depression ratings, serum homo-cysteine levels, hemoglobin A1c, and apolipoprotein e4 status. Age explained 4% of variance in δ, and through it, 11-18% of variance in future cognitive performance. Our findings suggest that normative aging is a dementing condition (i.e., a "senility"). While the majority of variance in dementia severity must be independent of age, age's specific effect is likely to accumulate over the lifespan. Our findings also constrain age's dementing effects on cognition to the age-related fraction of "general intelligence" (Spearman's "g"). That has broad biological and pathophysiological implications.

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J Gerontol A Biol Sci Med Sci. 2016 Feb 19. pii: glv212. [Epub ahead of print]

Gene Expression Differences Between Offspring of Long-Lived Individuals and Controls in Candidate Longevity Regions: Evidence for PAPSS2 as a Longevity Gene.

Yerges-Armstrong LM[1], Chai S[1], O'Connell JR[1], Curran JE[2], Blangero J[2], Mitchell BD[3], Shuldiner AR[3], Damcott CM[4].

Author information

Abstract

Although there is compelling evidence for a genetic contribution to longevity, identification of specific genes that robustly associate with longevity has been a challenge. In order to identify longevity-enhancing genes, we measured differential gene expression between offspring of long-lived Amish (older than 90 years; cases, n = 128) and spouses of these offspring (controls, n = 121) and correlated differentially expressed transcripts with locations of longevity-associated variants detected in a prior genome-wide association study (GWAS) of survival to age 90. Expression of one of these transcripts, 3'-phosphoadenosine 5'-phosphosulfate synthase 2 (PAPSS2), was significantly higher in offspring versus controls (4×10^{-4}) and this association was replicated using quantitative real-time polymerase chain reaction. PAPSS2, a sulfation enzyme located on chromosome 10, is ~80kb upstream of the PAPSS2 transcription start site. We found evidence of cis-expression for the originally reported GWAS SNP and PAPSS2. Monogenic conditions linked to PAPSS2 include andrenocortical androgen excess resulting in premature pubarche and skeletal dysplasias, both of which have premature aging features. In summary, these findings provide novel evidence for PAPSS2 as a longevity locus and illustrate the value of harnessing multiple "-omic" approaches to identify longevity candidates.

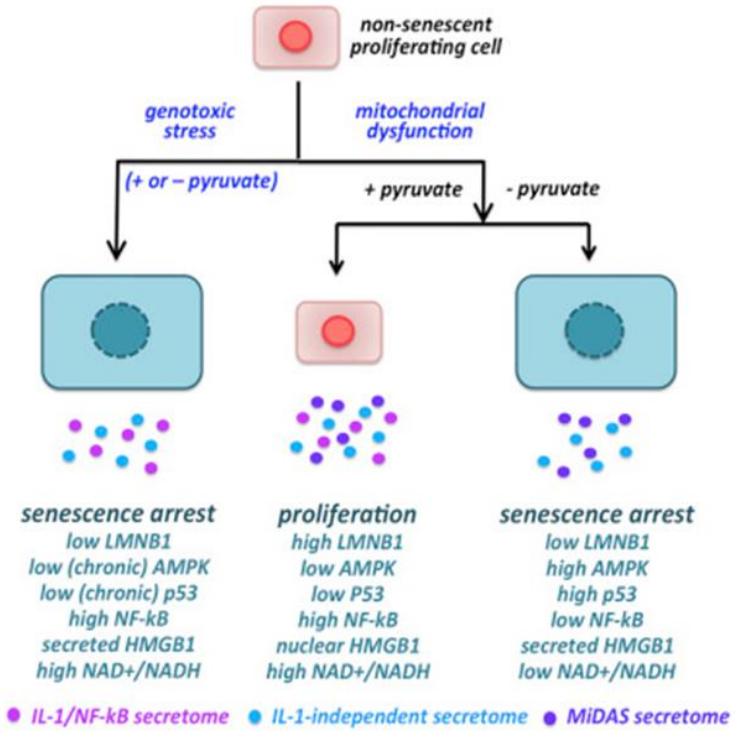
Mitochondrial Dysfunction Induces Senescence with a Distinct Secretory Phenotype

Christopher D. Wiley, Michael C. Velarde, Pacome Lecot, Su Liu, Ethan A. Sarnoski, Adam Freund, Kotaro Shirakawa, Hyung W. Lim, Sonnet S. Davis, Arvind Ramanathan, Akos A. Gerencser, Eric Verdin, Judith Campisi

Highlights

- Dysfunctional mitochondria cause cell senescence and a distinct secretory phenotype
- This secretory phenotype can influence the differentiation of certain cell types
- An NAD-AMPK-p53 pathway controls the secretory and mitotic arrest phenotypes
- Mice with dysfunctional mitochondria and premature aging accumulate senescent cells

Graphical Abstract



Summary

Cellular senescence permanently arrests cell proliferation, often accompanied by a multi-faceted senescence-associated secretory phenotype (SASP). Loss of mitochondrial function can drive age-related declines in the function of many post-mitotic tissues, but little is known about how mitochondrial dysfunction affects mitotic tissues. We show here that several manipulations that compromise mitochondrial function in proliferating human cells induce a senescence growth arrest with a modified SASP that lacks the IL-1-dependent inflammatory arm. Cells that underwent mitochondrial dysfunction-associated senescence (MiDAS) had lower NAD+/NADH ratios, which caused both the growth arrest and prevented the IL-1-associated SASP through AMPK-mediated p53 activation. Progeroid mice that rapidly accrue mtDNA mutations accumulated senescent cells with a MiDAS SASP in vivo, which suppressed adipogenesis and stimulated keratinocyte differentiation in cell culture. Our data identify a distinct senescence response and provide a mechanism by which mitochondrial dysfunction can drive aging phenotypes.

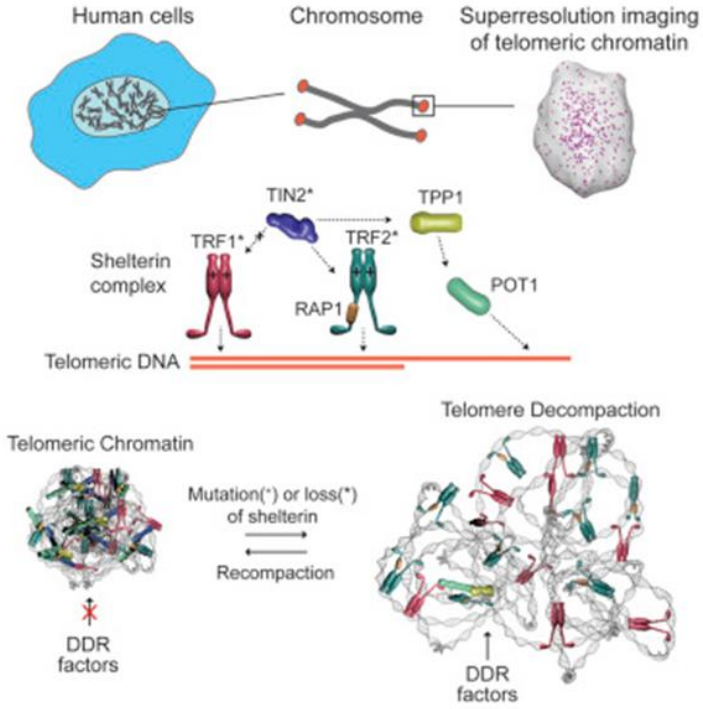
Shelterin Protects Chromosome Ends by Compacting Telomeric Chromatin

Jigar N. Bandaria, Peiwu Qin, Veysel Berk, Steven Chu, Ahmet Yildiz

Highlights

- Shelterin remodels telomeric chromatin into compact globular structures
- Telomeres decompact up to 10-fold upon the removal of shelterin subunits
- Decompacted telomeres become more accessible and recruit DDR signals
- Recompaction of telomeric chromatin prevents DDR accumulation

Graphical Abstract



Summary

Telomeres, repetitive DNA sequences at chromosome ends, are shielded against the DNA damage response (DDR) by the shelterin complex. To understand how shelterin protects telomere ends, we investigated the structural organization of telomeric chromatin in human cells using super-resolution microscopy. We found that telomeres form compact globular structures through a complex network of interactions between shelterin subunits and telomeric DNA, but not by DNA methylation, histone deacetylation, or histone trimethylation at telomeres and subtelomeric regions. Mutations that abrogate shelterin assembly or removal of individual subunits from telomeres cause up to a 10-fold increase in telomere volume. Decompacted telomeres accumulate DDR signals and become more accessible to telomere-associated proteins. Recompaction of telomeric chromatin using an orthogonal method displaces DDR signals from telomeres. These results reveal the chromatin remodeling activity of shelterin and demonstrate that shelterin-mediated compaction of telomeric chromatin provides robust protection of chromosome ends against the DDR machinery.

REVIEWS/COMMENTS/EDITORIALS

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inside the Cell

Open Access

Review Article

To clear, or not to clear (senescent cells)? That is the question

Amaia Lujambio[1,2,*]

Issue

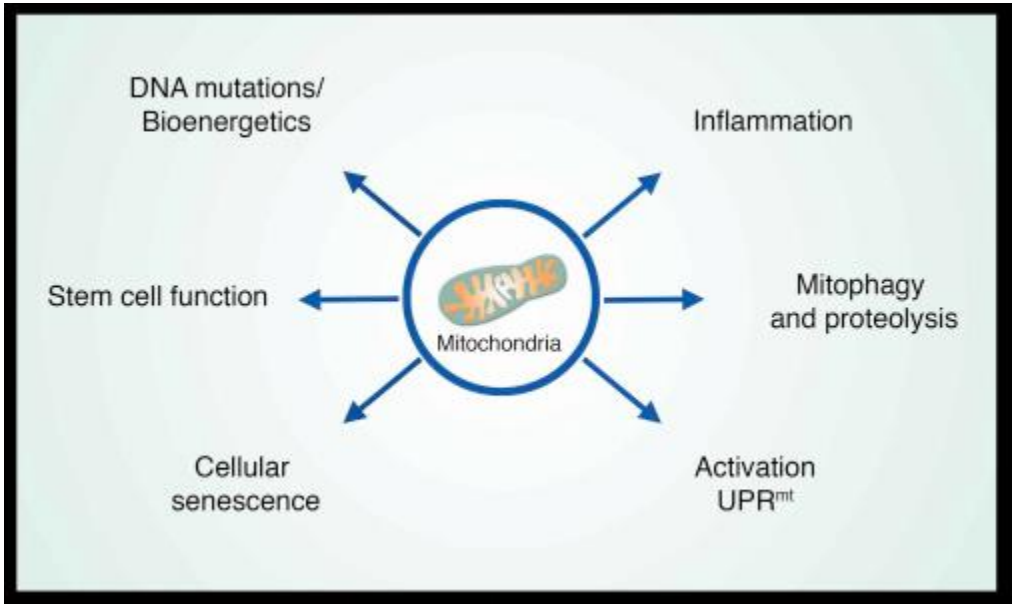
Abstract

Cellular senescence is an anti-proliferative program that restricts the propagation of cells subjected to different kinds of stress. Cellular senescence was initially described as a cell-autonomous tumor suppressor mechanism that triggers an irreversible cell cycle arrest that prevents the proliferation of damaged cells at risk of neoplastic transformation. However, discoveries during the last decade have established that senescent cells can also impact the surrounding tissue microenvironment and the neighboring cells in a non-cell-autonomous manner. These non-cell-autonomous activities are, in part, mediated by the selective secretion of extracellular matrix degrading enzymes, cytokines, chemokines and immune modulators, which collectively constitute the senescence-associated secretory phenotype. One of the key functions of the senescence-associated secretory phenotype is to attract immune cells, which in turn can orchestrate the elimination of senescent cells. Interestingly, the clearance of senescent cells seems to be critical to dictate the net effects of cellular senescence. As a general rule, the successful elimination of senescent cells takes place in processes that are considered beneficial, such as tumor suppression, tissue remodeling and embryonic development, while the chronic accumulation of senescent cells leads to more detrimental consequences, namely, cancer and aging. Nevertheless, exceptions to this rule may exist. Now that cellular senescence is in the spotlight for both anti-cancer and anti-aging therapies, understanding the precise underpinnings of senescent cell removal will be essential to exploit cellular senescence to its full potential.

The Mitochondrial Basis of Aging

Nuo Sun, Richard J. Youle, Toren Finkel

A decline in mitochondrial quality and activity has been associated with normal aging and correlated with the development of a wide range of age-related diseases. Here, we review the evidence that a decline in mitochondria function contributes to aging. In particular, we discuss how mitochondria contribute to specific aspects of the aging process, including cellular senescence, chronic inflammation, and the age-dependent decline in stem cell activity. Signaling pathways regulating the mitochondrial unfolded protein response and mitophagy are also reviewed, with particular emphasis placed on how these pathways might, in turn, regulate longevity. Taken together, these observations suggest that mitochondria influence or regulate a number of key aspects of aging and suggest that strategies directed at improving mitochondrial quality and function might have far-reaching beneficial effects.



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Oncotarget. 2016 Feb 23. doi: 10.18632/oncotarget.7645. [Epub ahead of print]

Reprogramming of energy metabolism as a driver of aging.

Feng Z[1], Hanson RW[2,3], Berger NA[2,3,4], Trubitsyn A[5].

Author information

Abstract

Aging is characterized by progressive loss of cellular function and integrity. It has been thought to be driven by stochastic molecular damage. However, genetic and environmental maneuvers enhancing mitochondrial function or inhibiting glycolysis extend lifespan and promote healthy aging in many species. In post-fertile Caenorhabditis elegans, a progressive decline in phosphoenolpyruvate carboxykinase with age, and a reciprocal increase in pyruvate kinase shunt energy metabolism from oxidative metabolism to anaerobic glycolysis. This reduces the efficiency and total of energy generation. As a result, energy-dependent physical activity and other cellular functions decrease due to unmatched energy demand and supply. In return, decrease in physical activity accelerates this metabolic shift, forming a vicious cycle. This metabolic event is a determinant of aging, and is retarded by caloric restriction to counteract aging. In this review, we summarize these and other evidence supporting the idea that metabolic reprogramming is a driver of aging. We also suggest strategies to test this hypothesis.

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Aging Cell

Review

The dark side of circulating nucleic acids

Silvia Gravina[1,†,*], John M. Sedivy[2] and Jan Vijg[1,*]

Issue

Summary

Free circulating or cell-free DNA (cfDNA), possibly from dying cells that release their contents into the blood as they break down, have become of major interest as a source for noninvasive diagnostics. Recent work demonstrated the uptake of human cfDNA in mouse cells *in vitro* and *in vivo*, accompanied by the activation of a cellular DNA damage response (DDR) and the appearance of apoptotic proteins in the host cells. By acting as a source of mobile genetic elements, cfDNA could be a continuous source of DNA mutagenesis of healthy cells in the body throughout life, promoting progressive cellular aging *in vivo*. As such, cfDNA may causally contribute to multiple aging-related diseases, such as cancer, diabetes, and Alzheimer's disease.

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Ann N Y Acad Sci. 2016 Feb 24. doi: 10.1111/nyas.13014. [Epub ahead of print]

Methionine restriction beyond life-span extension.

Ables GP[1], Hens JR[1], Nichenametla SN[1].

Author information

Abstract

Dietary methionine restriction (MR) extends life span across species via various intracellular regulatory mechanisms. In rodents, MR induces resistance against adiposity, improves hepatic glucose metabolism, preserves cardiac function, and reduces body size, all of which can affect the onset of age-related diseases. Recent studies have shown that MR-affected biomarkers, such as fibroblast growth factor 21, adiponectin, leptin, cystathionine β synthase, and insulin-like growth factor 1, can potentially alter physiology. The beneficial effects of MR could be explained in part by its ability to reduce mitochondrial oxidative stress. Studies have revealed that MR can reduce reactive oxygen species that damage cells and promote cancer progression. It has been demonstrated that either MR or the targeting of specific genes in the methionine cycle could induce cell apoptosis while decreasing proliferation in several cancer models. The complete mechanism underlying the actions of MR on the cell cycle during cancer has not been fully elucidated. Epigenetic mechanisms, such as methylation and noncoding RNAs, are also possible downstream effectors of MR; future studies should help to elucidate some of these mechanisms. Despite evidence that changes in dietary methionine can affect epigenetics, it remains unknown whether epigenetics is a mechanism in MR. This review summarizes research on MR and its involvement in metabolism, cancer, and epigenetics.

Front Genet. 2016 Feb 12;7:13. doi: 10.3389/fgene.2016.00013. eCollection 2016.

Cellular Senescence as the Causal Nexus of Aging.

Bhatia-Dey N[1], Kanherkar RR[1], Stair SE[2], Makarev EO[3], Csoka AB[4].

Author information

Abstract

In this paper we present cellular senescence as the ultimate driver of the aging process, as a "causal nexus" that bridges microscopic subcellular damage with the phenotypic, macroscopic effect of aging. It is important to understand how the various types of subcellular damage correlated with the aging process lead to the larger, visible effects of anatomical aging. While it has always been assumed that subcellular damage (cause) results in macroscopic aging (effect), the bridging link between the two has been hard to define. Here, we propose that this bridge, which we term the "causal nexus", is in fact cellular senescence. The subcellular damage itself does not directly cause the visible signs of aging, but rather, as the damage accumulates and reaches a critical mass, cells cease to proliferate and acquire the deleterious "senescence-associated secretory phenotype" (SASP) which then leads to the macroscopic consequences of tissue breakdown to create the physiologically aged phenotype. Thus senescence is a precondition for anatomical aging, and this explains why aging is a gradual process that remains largely invisible during most of its progression. The subcellular damage includes shortening of telomeres, damage to mitochondria, aneuploidy, and DNA double-strand breaks triggered by various genetic, epigenetic, and environmental factors. Damage pathways acting in isolation or in concert converge at the causal nexus of cellular senescence. In each species some types of damage can be more causative than in others and operate at a variable pace; for example, telomere erosion appears to be a primary cause in human cells, whereas activation of tumor suppressor genes is more causative in rodents. Such species-specific mechanisms indicate that despite different initial causes, most of aging is traced to a single convergent causal nexus: senescence. The exception is in some invertebrate species that escape senescence, and in non-dividing cells such as neurons, where senescence still occurs, but results in the SASP rather than loss of proliferation plus SASP. Aging currently remains an inevitable endpoint for most biological organisms, but the field of cellular senescence is primed for a renaissance and as our understanding of aging is refined, strategies capable of decelerating the aging process will emerge.

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Int J Cardiol. 2016 Feb 4;209:167-175. doi: 10.1016/j.ijcard.2016.02.039. [Epub ahead of print]

Healthy aging and myocardium: A complicated process with various effects in cardiac structure and physiology.

Nakou ES[1], Parthenakis FI[2], Kallergis EM[2], Marketou ME[2], Nakos KS[2], Vardas PE[2].

Author information

Abstract

It is known that there is an ongoing increase in life expectancy worldwide, especially in the population older than 65years of age. Cardiac aging is characterized by a series of complex pathophysiological changes affecting myocardium at structural, cellular, molecular and functional levels. These changes make the aged myocardium more susceptible to stress, leading to a high prevalence of cardiovascular diseases (heart failure, atrial fibrillation, left ventricular hypertrophy, coronary artery disease) in the elderly population. The aging process is genetically programmed but modified by environmental influences, so that the rate of aging can vary widely among people. We summarized the entire data concerning all the multifactorial changes in aged myocardium and highlighting the recent evidence for the pathophysiological basis of cardiac aging. Keeping an eye on the clinical side, this review will explore the potential implications of the age-related changes in the clinical management and on novel therapeutic strategies potentially deriving from the scientific knowledge currently acquired on cardiac aging process.