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Sven Bulterijs

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Generation and characterization of antibodies against arginine-derived advanced glycation endproducts

Tina Wang, Matthew D. Streeter, David A. Spiegel

Abstract

Although antibodies reagents have been widely employed for studying advanced glycation end-products (AGEs), these materials have been produced using complex mixtures of immunogens. Consequently, their epitope specificity remains unknown. Here we have generated the first antibodies capable of recognizing each of the three isomers of the methylglyoxal hydroimidazolones (MG-Hs) by using chemical synthesis to create homogenous immunogens. Furthermore, we have thoroughly characterized the epitope specificity of both our antibodies and that of two existing monoclonals by implementing a direct ELISA protocol employing synthetic MG-H antigens. Finally, we employed the reported anti-MG-H antibodies to the detection of MG-Hs in cellular systems using immunofluorescence microscopy. These studies have demonstrated that anti-MG-H1 and anti-MG-H3 staining is concentrated within the nucleus, while anti-MG-H2 affords only minimal signal. These observations are consistent with reported formation preferences for MG-Hs, and may suggest novel nuclear targets for non-enzymatic posttranslational modification. The antibody reagents reported herein, as well as the strategy employed for their creation, are likely to prove useful for the immunochemical study of AGEs in biological systems.

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Analysis of mammalian gene function through broad-based phenotypic screens across a consortium of mouse clinics

The function of the majority of genes in the mouse and human genomes remains unknown. The mouse embryonic stem cell knockout resource provides a basis for the characterization of relationships between genes and phenotypes. The EUMODIC consortium developed and validated robust methodologies for the broad-based phenotyping of knockouts through a pipeline comprising 20 disease-oriented platforms. We developed new statistical methods for pipeline design and data analysis aimed at detecting reproducible phenotypes with high power. We acquired phenotype data from 449 mutant alleles, representing 320 unique genes, of which half had no previous functional annotation. We captured data from over 27,000 mice, finding that 83% of the mutant lines are phenodeviant, with 65% demonstrating pleiotropy. Surprisingly, we found significant differences in phenotype annotation according to zygosity. New phenotypes were uncovered for many genes with previously unknown function, providing a powerful basis for hypothesis generation and further investigation in diverse systems.

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Programed Death is Favored by Natural Selection in Spatial Systems

Justin Werfel, Donald E. Ingber, and Yaneer Bar-Yam
Phys. Rev. Lett. **114**, 238103 – Published 12 June 2015

Article | References | No Citing Articles | Supplemental Material | PDF | HTML | Export Cita

ABSTRACT

Standard evolutionary theories of aging and mortality, implicitly based on mean-field assumptions, hold that programed mortality is untenable, as it opposes direct individual benefit. We show that in spatial models with local reproduction, programed deaths instead robustly result in long-term benefit to a lineage, by reducing local environmental resource depletion via spatiotemporal patterns causing feedback over many generations. Results are robust to model variations, implying that direct selection for shorter life span may be quite widespread in nature.

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KLF4-dependent phenotypic modulation of smooth muscle cells has a key role in atherosclerotic plaque pathogenesis

Previous studies investigating the role of smooth muscle cells (SMCs) and macrophages in the pathogenesis of atherosclerosis have provided controversial results owing to the use of unreliable methods for clearly identifying each of these cell types. Here, using *Myh11*-CreER^{T2} ROSA floxed STOP eYFP *Apoe*$^{-/-}$ mice to perform SMC lineage tracing, we find that traditional methods for detecting SMCs based on immunostaining for SMC markers fail to detect >80% of SMC-derived cells within advanced atherosclerotic lesions. These unidentified SMC-derived cells exhibit phenotypes of other cell lineages, including macrophages and mesenchymal stem cells (MSCs). SMC-specific conditional knockout of Krüppel-like factor 4 (*Klf4*) resulted in reduced numbers of SMC-derived MSC- and macrophage-like cells, a marked reduction in lesion size, and increases in multiple indices of plaque stability, including an increase in fibrous cap thickness as compared to wild-type controls. On the basis of *in vivo* KLF4 chromatin immunoprecipitation–sequencing (ChIP-seq) analyses and studies of cholesterol-treated cultured SMCs, we identified >800 KLF4 target genes, including many that regulate pro-inflammatory responses of SMCs. Our findings indicate that the contribution of SMCs to atherosclerotic plaques has been greatly underestimated, and that KLF4-dependent transitions in SMC phenotype are critical in lesion pathogenesis.

Lanosterol reverses protein aggregation in cataracts

The human lens is comprised largely of crystallin proteins assembled into a highly ordered, interactive macro-structure essential for lens transparency and refractive index. Any disruption of intra- or inter-protein interactions will alter this delicate structure, exposing hydrophobic surfaces, with consequent protein aggregation and cataract formation. Cataracts are the most common cause of blindness worldwide, affecting tens of millions of people[1], and currently the only treatment is surgical removal of cataractous lenses. The precise mechanisms by which lens proteins both prevent aggregation and maintain lens transparency are largely unknown. Lanosterol is an amphipathic molecule enriched in the lens. It is synthesized by lanosterol synthase (LSS) in a key cyclization reaction of a cholesterol synthesis pathway. Here we identify two distinct homozygous *LSS* missense mutations (W581R and G588S) in two families with extensive congenital cataracts. Both of these mutations affect highly conserved amino acid residues and impair key catalytic functions of LSS. Engineered expression of wild-type, but not mutant, *LSS* prevents intracellular protein aggregation of various cataract-causing mutant crystallins. Treatment by lanosterol, but not cholesterol, significantly decreased preformed protein aggregates both *in vitro* and in cell-transfection experiments. We further show that lanosterol treatment could reduce cataract severity and increase transparency in dissected rabbit cataractous lenses *in vitro* and cataract severity *in vivo* in dogs. Our study identifies lanosterol as a key molecule in the prevention of lens protein aggregation and points to a novel strategy for cataract prevention and treatment.

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Metabolic rescue in pluripotent cells from patients with mtDNA disease.

Ma H[1], Folmes CD[2], Wu J[3], Morey R[4], Mora-Castilla S[4], Ocampo A[3], Ma L[3], Poulton J[5], Wang X[6], Ahmed R[1], Kang E[1], Lee Y[1], Hayama T[1], Li Y[1], Van Dyken C[1], Gutierrez NM[1], Tippner-Hedges R[1], Koski A[1], Mitalipov N[1], Amato P[7], Wolf DP[8], Huang T[6], Terzic A[2], Laurent LC[4], Belmonte JC[3], Mitalipov S[1].

Author information

Abstract

Mitochondria have a major role in energy production via oxidative phosphorylation, which is dependent on the expression of critical genes encoded by mitochondrial (mt)DNA. Mutations in mtDNA can cause fatal or severely debilitating disorders with limited treatment options. Clinical manifestations vary based on mutation type and heteroplasmy (that is, the relative levels of mutant and wild-type mtDNA within each cell). Here we generated genetically corrected pluripotent stem cells (PSCs) from patients with mtDNA disease. Multiple induced pluripotent stem (iPS) cell lines were derived from patients with common heteroplasmic mutations including 3243A>G, causing mitochondrial encephalomyopathy and stroke-like episodes (MELAS), and 8993T>G and 13513G>A, implicated in Leigh syndrome. Isogenic MELAS and Leigh syndrome iPS cell lines were generated containing exclusively wild-type or mutant mtDNA through spontaneous segregation of heteroplasmic mtDNA in proliferating fibroblasts. Furthermore, somatic cell nuclear transfer (SCNT) enabled replacement of mutant mtDNA from homoplasmic 8993T>G fibroblasts to generate corrected Leigh-NT1 PSCs. Although Leigh-NT1 PSCs contained donor oocyte wild-type mtDNA (human haplotype D4a) that differed from Leigh syndrome patient haplotype (F1a) at a total of 47 nucleotide sites, Leigh-NT1 cells displayed transcriptomic profiles similar to those in embryo-derived PSCs carrying wild-type mtDNA, indicative of normal nuclear-to-mitochondrial interactions. Moreover, genetically rescued patient PSCs displayed normal metabolic function compared to impaired oxygen consumption and ATP production observed in mutant cells. We conclude that both reprogramming approaches offer complementary strategies for derivation of PSCs containing exclusively wild-type mtDNA, through spontaneous segregation of heteroplasmic mtDNA in individual iPS cell lines or mitochondrial replacement by SCNT in homoplasmic mtDNA-based disease.

β2-microglobulin is a systemic pro-aging factor that impairs cognitive function and neurogenesis

Aging drives cognitive and regenerative impairments in the adult brain, increasing susceptibility to neurodegenerative disorders in healthy individuals[1, 2, 3, 4]. Experiments using heterochronic parabiosis, in which the circulatory systems of young and old animals are joined, indicate that circulating pro-aging factors in old blood drive aging phenotypes in the brain[5, 6]. Here we identify β2-microglobulin (B2M), a component of major histocompatibility complex class 1 (MHC I) molecules, as a circulating factor that negatively regulates cognitive and regenerative function in the adult hippocampus in an age-dependent manner. B2M is elevated in the blood of aging humans and mice, and it is increased within the hippocampus of aged mice and young heterochronic parabionts. Exogenous B2M injected systemically, or locally in the hippocampus, impairs hippocampal-dependent cognitive function and neurogenesis in young mice. The negative effects of B2M and heterochronic parabiosis are, in part, mitigated in the hippocampus of young transporter associated with antigen processing 1 (*Tap1*)-deficient mice with reduced cell surface expression of MHC I. The absence of endogenous B2M expression abrogates age-related cognitive decline and enhances neurogenesis in aged mice. Our data indicate that systemic B2M accumulation in aging blood promotes age-related cognitive dysfunction and impairs neurogenesis, in part via MHC I, suggesting that B2M may be targeted therapeutically in old age.

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Proc Natl Acad Sci U S A. 2015 Jul 21;112(29):8993-8. doi: 10.1073/pnas.1421942112. Epub 2015 Jul 6.

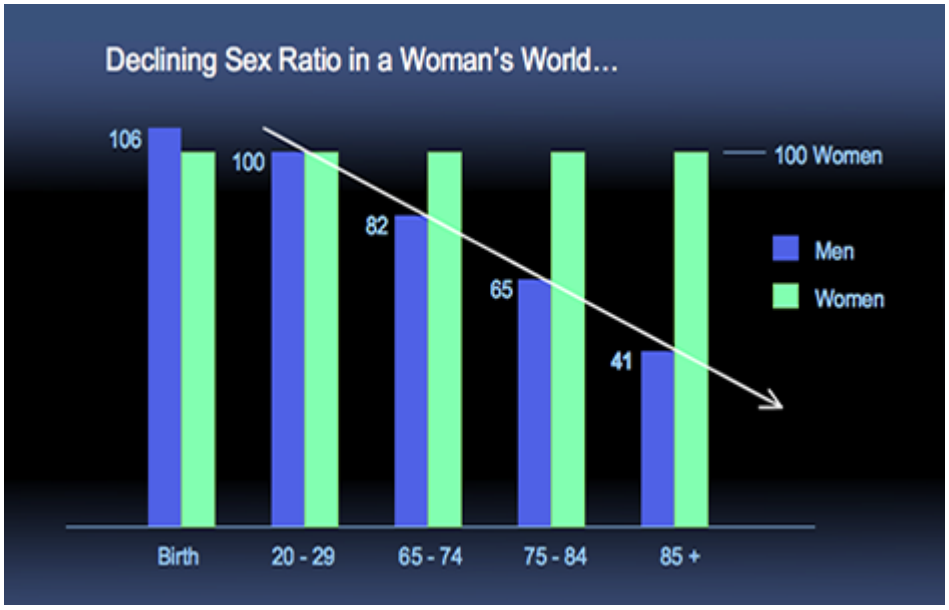
Twentieth century surge of excess adult male mortality.

Beltrán-Sánchez H[1], Finch CE[2], Crimmins EM[2].

⊕ Author information

Abstract

Using historical data from 1,763 birth cohorts from 1800 to 1935 in 13 developed countries, we show that what is now seen as normal-a large excess of female life expectancy in adulthood-is a demographic phenomenon that emerged among people born in the late 1800s. We show that excess adult male mortality is clearly rooted in specific age groups, 50-70, and that the sex asymmetry emerged in cohorts born after 1880 when male:female mortality ratios increased by as much as 50% from a baseline of about 1.1. Heart disease is the main condition associated with increased excess male mortality for those born after 1900. We further show that smoking-attributable deaths account for about 30% of excess male mortality at ages 50-70 for cohorts born in 1900-1935. However, after accounting for smoking, substantial excess male mortality at ages 50-70 remained, particularly from cardiovascular disease. The greater male vulnerability to cardiovascular conditions emerged with the reduction in infectious mortality and changes in health-related behaviors.



Graph source: http://transgenerational.org/aging/demographics.htm

Neural activity and CaMKII protect mitochondria from fragmentation in aging *Caenorhabditis elegans* neurons

Decline in mitochondrial morphology and function is a hallmark of neuronal aging. Here we report that progressive mitochondrial fragmentation is a common manifestation of aging *Caenorhabditis elegans* neurons and body wall muscles. We show that sensory-evoked activity was essential for maintaining neuronal mitochondrial morphology, and this activity-dependent mechanism required the Degenerin/ENaC sodium channel MEC-4, the L-type voltage-gated calcium channel EGL-19, and the Ca/calmodulin-dependent kinase II (CaMKII) UNC-43. Importantly, UNC-43 phosphorylated and inhibited the dynamin-related protein (DRP)-1, which was responsible for excessive mitochondrial fragmentation in neurons that lacked sensory-evoked activity. Moreover, enhanced activity in the aged neurons ameliorated mitochondrial fragmentation. These findings provide a detailed description of mitochondrial behavior in aging neurons and identify activity-dependent DRP-1 phosphorylation by CaMKII as a key mechanism in neuronal mitochondrial maintenance.

Systematic Aβ Analysis in *Drosophila* Reveals High Toxicity for the 1-42, 3-42 and 11-42 Peptides, and Emphasizes N- and C-Terminal Residues

Brain amyloid plaques are a hallmark of Alzheimer's disease (AD), and primarily consist of aggregated Aβ peptides. While Aβ 1-40 and Aβ 1-42 are the most abundant, a number of other Aβ peptides have also been identified. Studies have indicated differential toxicity for these various Aβ peptides, but *in vivo* toxicity has not been systematically tested. To address this issue, we generated improved transgenic *Drosophila UAS* strains expressing 11 pertinent Aβ peptides. *UAS* transgenic flies were generated by identical chromosomal insertion, hence removing any transgenic position effects, and crossed to a novel and robust *Gal4* driver line. Using this improved *Gal4/UAS* set-up, survival and activity assays revealed that Aβ 1-42 severely shortens lifespan and reduces activity. N-terminal truncated peptides were quite toxic, with 3-42 similar to 1-42, while 11-42 showed a pronounced but less severe phenotype. N-terminal mutations in 3-42 (E3A) or 11-42 (E11A) resulted in reduced toxicity for 11-42, and reduced aggregation for both variants. Strikingly, C-terminal truncation of Aβ (1-41, -40, -39, -38, -37) were non-toxic. In contrast, C-terminal extension to 1-43 resulted in reduced lifespan and activity, but not to the same extent as 1-42. Mutating residue 42 in 1-42 (A42D, A42R and A42W) greatly reduced Aβ accumulation and toxicity. Histological and biochemical analysis revealed strong correlation between *in vivo* toxicity and brain Aβ aggregate load, as well as amount of insoluble Aβ. This systematic *Drosophila in vivo* and *in vitro* analysis reveals crucial N- and C-terminal specificity for Aβ neurotoxicity and aggregation, and underscores the importance of residues 1-10 and E11, as well as a pivotal role of A42.

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Age-Related Gene Expression Differences in Monocytes from Human Neonates, Young Adults, and Older Adults

A variety of age-related differences in the innate and adaptive immune systems have been proposed to contribute to the increased susceptibility to infection of human neonates and older adults. The emergence of RNA sequencing (RNA-seq) provides an opportunity to obtain an unbiased, comprehensive, and quantitative view of gene expression differences in defined cell types from different age groups. An examination of *ex vivo* human monocyte responses to lipopolysaccharide stimulation or *Listeria monocytogenes* infection by RNA-seq revealed extensive similarities between neonates, young adults, and older adults, with an unexpectedly small number of genes exhibiting statistically significant age-dependent differences. By examining the differentially induced genes in the context of transcription factor binding motifs and RNA-seq data sets from mutant mouse strains, a previously described deficiency in interferon response factor-3 activity could be implicated in most of the differences between newborns and young adults. Contrary to these observations, older adults exhibited elevated expression of inflammatory genes at baseline, yet the responses following stimulation correlated more closely with those observed in younger adults. Notably, major differences in the expression of constitutively expressed genes were not observed, suggesting that the age-related differences are driven by environmental influences rather than cell-autonomous differences in monocyte development.

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Oncotarget. 2015 Jun 30;6(18):15902-30.

The effects of graded levels of calorie restriction: I. impact of short term calorie and protein restriction on body composition in the C57BL/6 mouse.

Mitchell SE[1], Tang Z[1], Kerbois C[1], Delville C[1], Konstantopedos P[1], Bruel A[1], Derous D[1], Green C[1], Aspden RM[2], Goodyear SR[2], Chen L[3], Han JJ[4], Wang Y[5], Promislow DE[6], Lusseau D[1], Douglas A[1], Speakman JR[1,5].

⊕ Author information

Abstract

Faced with reduced levels of food, animals must adjust to the consequences of the shortfall in energy. We explored how C57BL/6 mice withdrew energy from different body tissues during three months of food restriction at graded levels up to 40% (calorie restriction: CR). We compared this to the response to equivalent levels of protein restriction (PR) without a shortfall in calories. Under CR there was a dynamic change in body mass over 30 days and thereafter it stabilized. The time to reach stability was independent of the level of restriction. At the end of three months whole body dissections revealed differential utilization of the different tissues. Adipose tissue depots were the most significantly utilized tissue, and provided 55.8 to 60.9% of the total released energy. In comparison, reductions in the sizes of structural tissues contributed between 29.8 and 38.7% of the energy. The balance was made up by relatively small changes in the vital organs. The components of the alimentary tract grew slightly under restriction, particularly the stomach, and this was associated with a parallel increase in assimilation efficiency of the food (averaging 1.73%). None of the changes under CR were recapitulated by equivalent levels of PR.

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Acrylamide induces accelerated endothelial aging in a human cell model

Acrylamide (AAM) has been recently discovered in food as a Maillard reaction product. AAM and glycidamide (GA), its metabolite, have been described as probably carcinogenic to humans. It is widely established that senescence and carcinogenicity are closely related. *In vitro*, endothelial aging is characterized by replicative senescence in which primary cells in culture lose their ability to divide.

Our objective was to assess the effects of AAM and GA on human endothelial cell senescence.

Human umbilical vein endothelial cells (HUVECs) cultured *in vitro* were used as model. HUVECs were cultured over 3 months with AAM or GA (1, 10 or 100 µM) until growth arrest. To analyze senescence, β-galactosidase activity and telomere length of HUVECs were measured by cytometry and semi-quantitative PCR, respectively.

At all tested concentrations, AAM or GA reduced cell population doubling compared to the control condition ($p < 0.001$). β-galactosidase activity in endothelial cells was increased when exposed to AAM (≥10 µM) or GA (≥1 µM) ($p < 0.05$). AAM (≥10 µM) or GA (100 µM) accelerated telomere shortening in HUVECs ($p < 0.05$).

In conclusion, *in vitro* chronic exposure to AAM or GA at low concentrations induces accelerated senescence. This result suggests that an exposure to AAM might contribute to endothelial aging.

PLoS One. 2015 Jul 29;10(7):e0133923. doi: 10.1371/journal.pone.0133923. eCollection 2015.

Calorie Restriction Suppresses Age-Dependent Hippocampal Transcriptional Signatures.

Schafer MJ[1], Dolgalev I[2], Alldred MJ[3], Heguy A[4], Ginsberg SD[5].

Author information

Abstract

Calorie restriction (CR) enhances longevity and mitigates aging phenotypes in numerous species. Physiological responses to CR are cell-type specific and variable throughout the lifespan. However, the mosaic of molecular changes responsible for CR benefits remains unclear, particularly in brain regions susceptible to deterioration during aging. We examined the influence of long-term CR on the CA1 hippocampal region, a key learning and memory brain area that is vulnerable to age-related pathologies, such as Alzheimer's disease (AD). Through mRNA sequencing and NanoString nCounter analysis, we demonstrate that one year of CR feeding suppresses age-dependent signatures of 882 genes functionally associated with synaptic transmission-related pathways, including calcium signaling, long-term potentiation (LTP), and Creb signaling in wild-type mice. By comparing the influence of CR on hippocampal CA1 region transcriptional profiles at younger-adult (5 months, 2.5 months of feeding) and older-adult (15 months, 12.5 months of feeding) timepoints, we identify conserved upregulation of proteome quality control and calcium buffering genes, including heat shock 70 kDa protein 1b (Hspa1b) and heat shock 70 kDa protein 5 (Hspa5), protein disulfide isomerase family A member 4 (Pdia4) and protein disulfide isomerase family A member 6 (Pdia6), and calreticulin (Calr). Expression levels of putative neuroprotective factors, klotho (Kl) and transthyretin (Ttr), are also elevated by CR in adulthood, although the global CR-specific expression profiles at younger and older timepoints are highly divergent. At a previously unachieved resolution, our results demonstrate conserved activation of neuroprotective gene signatures and broad CR-suppression of age-dependent hippocampal CA1 region expression changes, indicating that CR functionally maintains a more youthful transcriptional state within the hippocampal CA1 sector.

Proc Natl Acad Sci U S A. 2015 Jul 28;112(30):9364-9. doi: 10.1073/pnas.1510328112. Epub 2015 Jul 13.

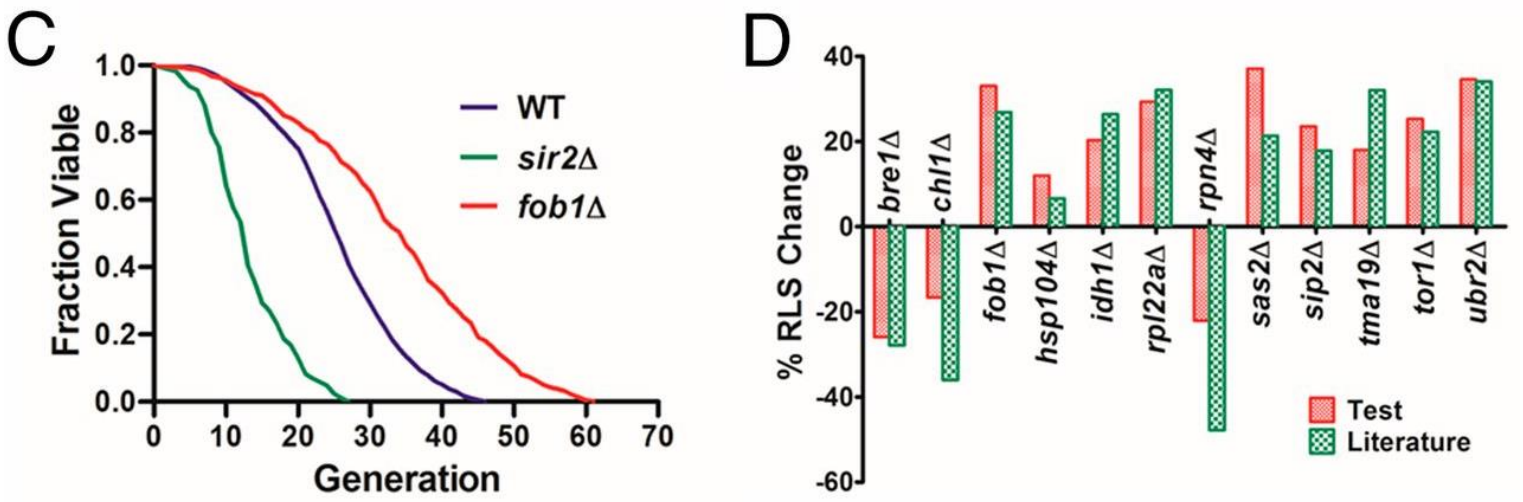
High-throughput analysis of yeast replicative aging using a microfluidic system.

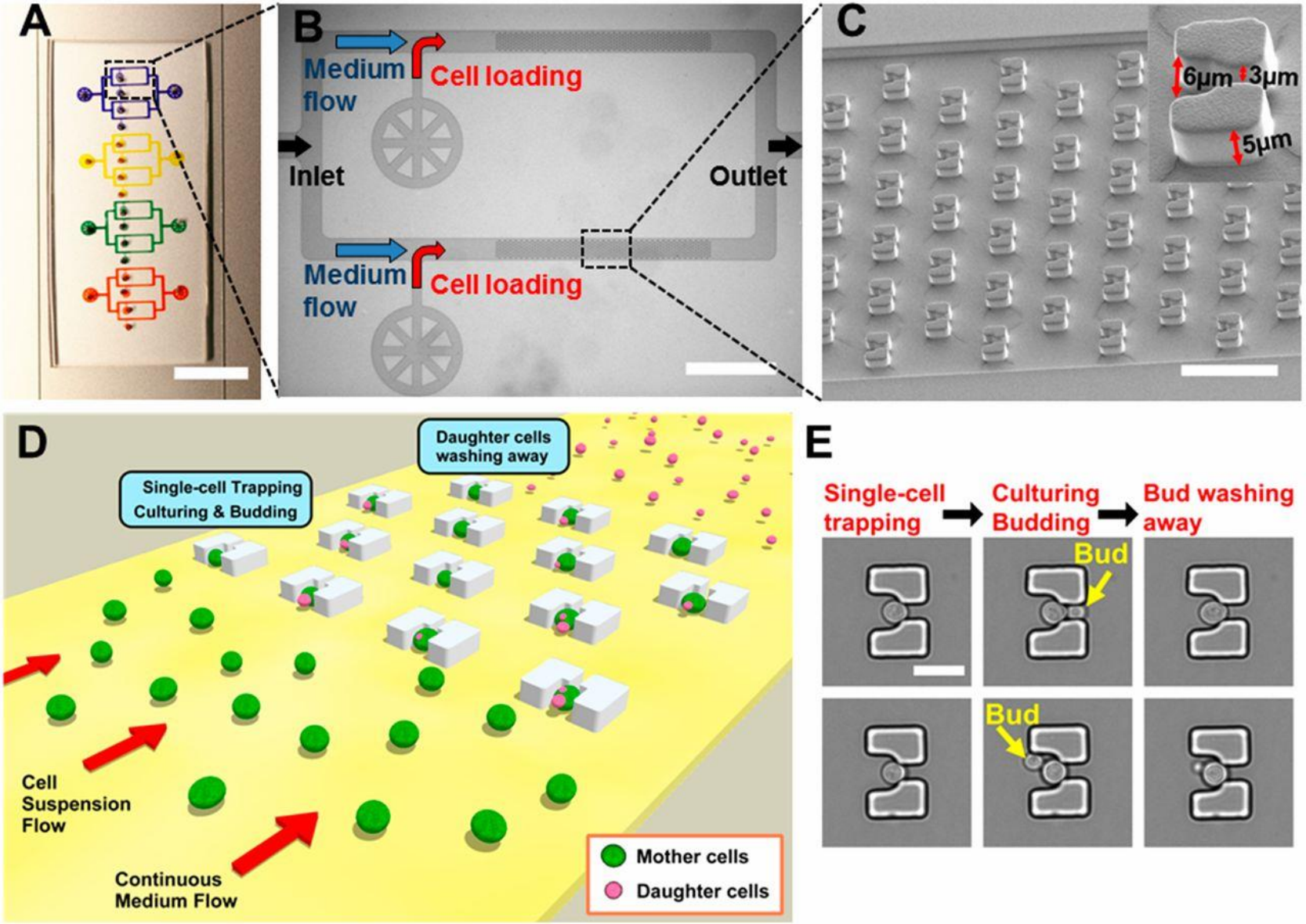
Jo MC[1], Liu W[2], Gu L[3], Dang W[4], Qin L[5].

Author information

Abstract

Saccharomyces cerevisiae has been an important model for studying the molecular mechanisms of aging in eukaryotic cells. However, the laborious and low-throughput methods of current yeast replicative lifespan assays limit their usefulness as a broad genetic screening platform for research on aging. We address this limitation by developing an efficient, high-throughput microfluidic single-cell analysis chip in combination with high-resolution time-lapse microscopy. This innovative design enables, to our knowledge for the first time, the determination of the yeast replicative lifespan in a high-throughput manner. Morphological and phenotypical changes during aging can also be monitored automatically with a much higher throughput than previous microfluidic designs. We demonstrate highly efficient trapping and retention of mother cells, determination of the replicative lifespan, and tracking of yeast cells throughout their entire lifespan. Using the high-resolution and large-scale data generated from the high-throughput yeast aging analysis (HYAA) chips, we investigated particular longevity-related changes in cell morphology and characteristics, including critical cell size, terminal morphology, and protein subcellular localization. In addition, because of the significantly improved retention rate of yeast mother cell, the HYAA-Chip was capable of demonstrating replicative lifespan extension by calorie restriction.




A
B
Medium flow
Cell loading
Inlet
Outlet
Medium flow
Cell loading
C
6μm
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D
Daughter cells washing away
Single-cell Trapping Culturing & Budding
Cell Suspension Flow
Continuous Medium Flow
Mother cells
Daughter cells
E
Single-cell trapping
Culturing Budding
Bud washing away
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PDGFRβ signalling regulates local inflammation and synergizes with hypercholesterolaemia to promote atherosclerosis

Platelet-derived growth factor (PDGF) is a mitogen and chemoattractant for vascular smooth muscle cells (VSMCs). However, the direct effects of PDGF receptor β (PDGFRβ) activation on VSMCs have not been studied in the context of atherosclerosis. Here we present a new mouse model of atherosclerosis with an activating mutation in PDGFRβ. Increased PDGFRβ signalling induces chemokine secretion and leads to leukocyte accumulation in the adventitia and media of the aorta. Furthermore, PDGFRβ^{D849V} amplifies and accelerates atherosclerosis in hypercholesterolemic *ApoE*$^{-/-}$ or *Ldlr*$^{-/-}$ mice. Intriguingly, increased PDGFRβ signalling promotes advanced plaque formation at novel sites in the thoracic aorta and coronary arteries. However, deletion of the PDGFRβ-activated transcription factor STAT1 in VSMCs alleviates inflammation of the arterial wall and reduces plaque burden. These results demonstrate that PDGFRβ pathway activation has a profound effect on vascular disease and support the conclusion that inflammation in the outer arterial layers is a driving process for atherosclerosis.

Autophagy and mTORC1 regulate the stochastic phase of somatic cell reprogramming

We describe robust induction of autophagy during the reprogramming of mouse fibroblasts to induced pluripotent stem cells by four reprogramming factors (Sox2, Oct4, Klf4 and c-Myc), henceforth 4F. This process occurs independently of p53 activation, and is mediated by the synergistic downregulation of mechanistic target of rapamycin complex 1 (mTORC1) and the induction of autophagy-related genes. The 4F coordinately repress mTORC1, but bifurcate in their regulation of autophagy-related genes, with Klf4 and c-Myc inducing them but Sox2 and Oct4 inhibiting them. On one hand, inhibition of mTORC1 facilitates reprogramming by promoting cell reshaping (mitochondrial remodelling and cell size reduction). On the other hand, mTORC1 paradoxically impairs reprogramming by triggering autophagy. Autophagy does not participate in cell reshaping in reprogramming but instead degrades p62, whose accumulation in autophagy-deficient cells facilitates reprogramming. Our results thus reveal a complex signalling network involving mTORC1 inhibition and autophagy induction in the early phase of reprogramming, whose delicate balance ultimately determines reprogramming efficiency.

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Aging Cell. 2015 Jul 14. doi: 10.1111/acel.12373. [Epub ahead of print]

Circulating microRNA signature of genotype-by-age interactions in the long-lived Ames dwarf mouse.

Victoria B[1], Dhahbi JM[2,3], Nunez Lopez YO[4], Spinel L[1], Atamna H[5], Spindler SR[2], Masternak MM[1,6].

Author information

Abstract

Recent evidence demonstrates that serum levels of specific miRNAs significantly change with age. The ability of circulating sncRNAs to act as signaling molecules and regulate a broad spectrum of cellular functions implicates them as key players in the aging process. To discover circulating sncRNAs that impact aging in the long-lived Ames dwarf mice, we conducted deep sequencing of small RNAs extracted from serum of young and old mice. Our analysis showed genotype-specific changes in the circulating levels of 21 miRNAs during aging [genotype-by-age interaction (GbA)]. Genotype-by-age miRNAs showed four distinct expression patterns and significant overtargeting of transcripts involved in age-related processes. Functional enrichment analysis of putative and validated miRNA targets highlighted cellular processes such as tumor suppression, anti-inflammatory response, and modulation of Wnt, insulin, mTOR, and MAPK signaling pathways, among others. The comparative analysis of circulating GbA miRNAs in Ames mice with circulating miRNAs modulated by calorie restriction (CR) in another long-lived mouse suggests CR-like and CR-independent mechanisms contributing to longevity in the Ames mouse. In conclusion, we showed for the first time a signature of circulating miRNAs modulated by age in the long-lived Ames mouse.

KEYWORDS: aging; circulating miRNAs; dwarf mouse; sequencing; sncRNAs; tRNA halves

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Longevity Is Linked to Mitochondrial Mutation Rates in Rockfish: A Test Using Poisson Regression

The mitochondrial theory of ageing proposes that the cumulative effect of biochemical damage in mitochondria causes mitochondrial mutations and plays a key role in ageing. Numerous studies have applied comparative approaches to test one of the predictions of the theory: That the rate of mitochondrial mutations is negatively correlated with longevity. Comparative studies face three challenges in detecting correlates of mutation rate: Covariation of mutation rates between species due to ancestry, covariation between life-history traits, and difficulty obtaining accurate estimates of mutation rate. We address these challenges using a novel Poisson regression method to examine the link between mutation rate and lifespan in rockfish (*Sebastes*). This method has better performance than traditional sister-species comparisons when sister species are too recently diverged to give reliable estimates of mutation rate. Rockfish are an ideal model system: They have long life spans with indeterminate growth and little evidence of senescence, which minimizes the confounding tradeoffs between lifespan and fecundity. We show that lifespan in rockfish is negatively correlated to rate of mitochondrial mutation, but not the rate of nuclear mutation. The life history of rockfish allows us to conclude that this relationship is unlikely to be driven by the tradeoffs between longevity and fecundity, or by the frequency of DNA replications in the germline. Instead, the relationship is compatible with the hypothesis that mutation rates are reduced by selection in long-lived taxa to reduce the chance of mitochondrial damage over its lifespan, consistent with the mitochondrial theory of ageing.

Brain Res Bull. 2015 Jul;116:67-72. doi: 10.1016/j.brainresbull.2015.06.004. Epub 2015 Jun 29.

Effect of caloric restriction on the SIRT1/mTOR signaling pathways in senile mice.

Ma L[1], Dong W[2], Wang R[3], Li Y[4], Xu B[5], Zhang J[2], Zhao Z[2], Wang Y[2].

Author information

Abstract

AIMS: To determine the effects and underlying molecular mechanisms of caloric restriction (CR) in C57BL/6 mice.

METHODS: Thirty-six 6-week-old male C57BL/6 mice were assigned to a normal control group (NC, n=12), a high energy group (HE, n=12), and a CR group (n=12), and received a normal diet, a high-calorie diet, or a calorie-restricted diet, respectively, for 44 weeks. Body weight and serum glucose concentration were regularly recorded, and animals were sacrificed and hippocampus tissues were collected for immunohistochemistry (n=6 per group), western blotting (n=3 per group) and real-time polymerase chain reaction (n=3 per group) analysis at the end of the 44-week experimental period. Immunohistochemistry, western blotting and real-time polymerase chain reaction were used to detect changes in hippocampal proteins may be involved in the SIRT1/mTOR pathways.

RESULTS: Body weight and serum glucose over the 44 weeks in animals from the CR group were lower than those of HE group. The number of SIRT1-immunoreactive cells in the CR group was significantly higher than in the NC and HE groups, and SIRT1 mRNA expression in the CR group was significantly higher than that in the HE group, but there was no difference in SIRT1 protein expression among the three groups. mTOR and S6K1 protein activation and mTOR and S6K1 mRNA were significantly lower in the CR group than in the NC group.

CONCLUSIONS: Our findings suggest that a CR diet could lead to activation of SIRT1 and suppression of mTOR and S6K1 activation in C57BL/6 mice. We have shown that the SIRT1/mTOR signaling pathways may be involved in the neuroprotective effect of CR.

KEYWORDS: Caloric restriction; S6K1; SIRT1; mTOR

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Aging (Albany NY). 2015 Jun;7(6):383-8.

High-glucose diets have sex-specific effects on aging in C. elegans: toxic to hermaphrodites but beneficial to males.

Liggett MR[1], Hoy MJ[1], Mastroianni M[1], Mondoux MA[1].

Author information

Abstract

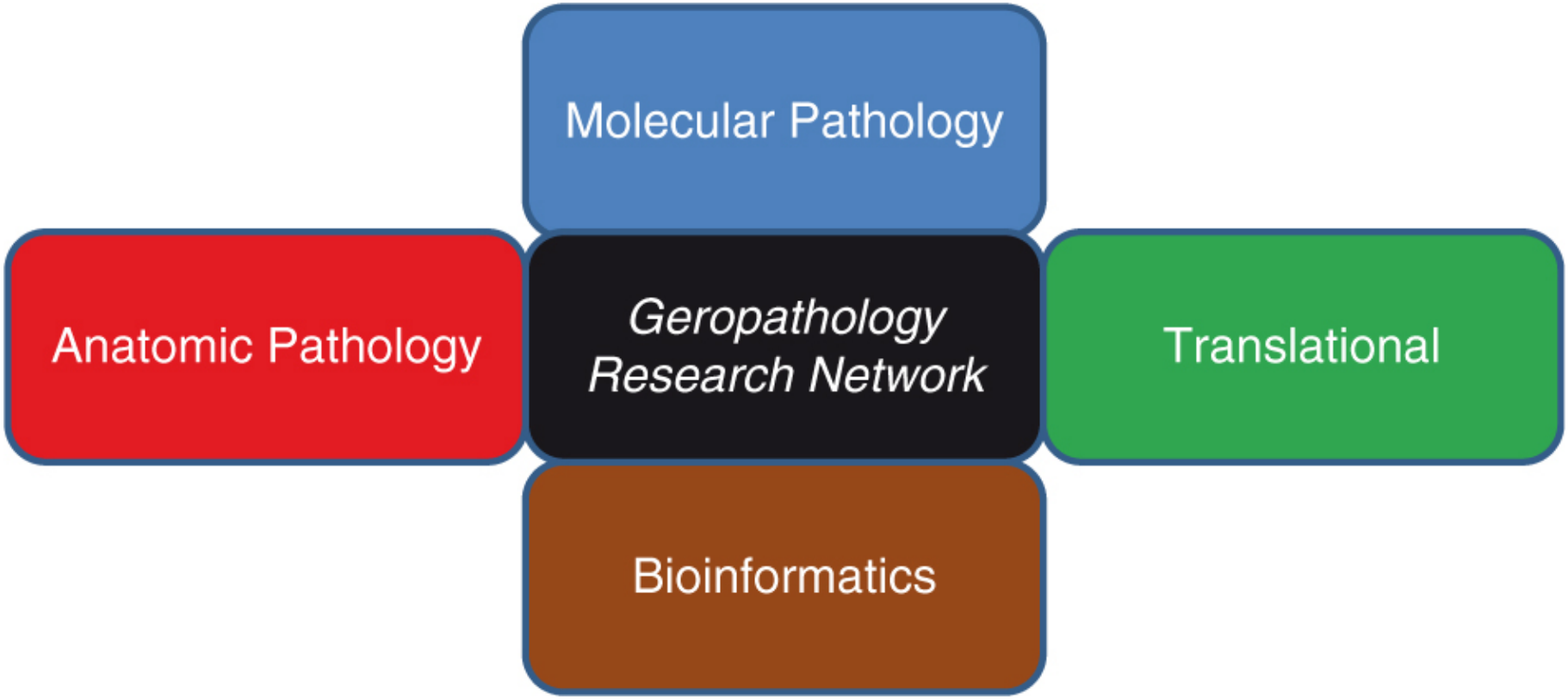
Diet and sex are important determinants of lifespan. In humans, high sugar diets, obesity, and type 2 diabetes correlate with decreased lifespan, and females generally live longer than males. The nematode Caenorhabditis elegans is a classical model for aging studies, and has also proven useful for characterizing the response to high-glucose diets. However, studies on male animals are lacking. We found a surprising dichotomy: glucose regulates lifespan and aging in a sex-specific manner, with beneficial effects on males compared to toxic effects on hermaphrodites. High-glucose diet resulted in greater mobility with age for males, along with a modest increase in median lifespan. In contrast, high-glucose diets decrease both lifespan and mobility for hermaphrodites. Understanding sex-specific responses to high-glucose diets will be important for determining which evolutionarily conserved glucose-responsive pathways that regulate aging are "universal" and which are likely to be cell-type or sex-specific.

KEYWORDS: C. elegans; glucose; healthspan; mobility; sex specificity

Reviews/Editorials/Commentaries

Geropathology Research Network Symposium 2015

"Geriatric scientists and pathologists convened in Seattle, WA, on May 7 and 8, 2015, for the first annual symposium of the Geropathology Research Network. The network is a newly formed consortium (Fig. 1) supported by the United States National Institutes of Health (NIH). The mission of the network is to develop ways to translationally enhance the level, scope, and consistency of molecular and anatomic pathology assessment in old animals involved in aging studies using a network of pathologists and scientists with expertise in the pathobiology of aging."



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Interventions to Slow Aging in Humans: Are We Ready?

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Author information

Abstract

The workshop entitled 'Interventions to Slow Aging in Humans: Are We Ready?' was held in Erice, Italy, on October 8-13, 2013, to bring together leading experts in the biology and genetics of aging and obtain a consensus related to the discovery and development of safe interventions to slow aging and increase healthy lifespan in humans. There was consensus that there is sufficient evidence that aging interventions will delay and prevent disease onset for many chronic conditions of adult and old age. Essential pathways have been identified, and behavioral, dietary, and pharmacologic approaches have emerged. Although many gene targets and drugs were discussed and there was not complete consensus about all interventions, the participants selected a subset of the most promising strategies that could be tested in humans for their effects on healthspan. These were: (i) dietary interventions mimicking chronic dietary restriction (periodic fasting mimicking diets, protein restriction, etc.); (ii) drugs that inhibit the growth hormone/IGF-I axis; (iii) drugs that inhibit the mTOR-S6K pathway; or (iv) drugs that activate AMPK or specific sirtuins. These choices were based in part on consistent evidence for the pro-longevity effects and ability of these interventions to prevent or delay multiple age-related diseases and improve healthspan in simple model organisms and rodents and their potential to be safe and effective in extending human healthspan. The authors of this manuscript were speakers and discussants invited to the workshop. The following summary highlights the major points addressed and the conclusions of the meeting.

Ageing Res Rev. 2015 Jun 17. pii: S1568-1637(15)00033-1. doi: 10.1016/j.arr.2015.03.005. [Epub ahead of print]

Aging: A deficiency state involving declining angiogenic factors.

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Author information

Abstract

This essay begins by proposing that muscle weakness of old age from sarcopenia is due in large part to reduced capillary density in the muscles, as documented in 9 reports of aged persons and animals. Capillary density (CD) is determined by local levels of various angiogenic factors, which also decline in muscles with aging, as reported in 7 studies of old persons and animals. There are also numerous reports of reduced CD in the aged brain and other studies showing reduced CD in the kidney and heart of aged animals. Thus a waning angiogenesis throughout the body may be a natural occurrence in later years and may account significantly for the lesser ailments (physical and cognitive) of elderly people. Old age is regarded here as a deficiency state which may be corrected by therapeutic angiogenesis, much as a hormonal deficiency can be relieved by the appropriate hormone therapy. Such therapy could employ recombinant angiogenic factors which are now commercially available.

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Ann N Y Acad Sci. 2015 Jul 27. doi: 10.1111/nyas.12834. [Epub ahead of print]

Manipulation of health span and function by dietary caloric restriction mimetics.

Roth GS[1], Ingram DK[2].

⊕ Author information

Abstract

After nearly a century of rigorous investigation and testing, dietary caloric restriction (CR) remains the most robust and reproducible method for slowing aging and maintaining health, function, and vitality. This intervention has been applied to species across the evolutionary spectrum, but for a number of reasons, practical applicability to humans has been questioned. To overcome these issues, we initiated the field of CR mimetics in 1998 and have observed its development into a full-fledged antiaging industry. Basically, strategies that enable individuals to obtain the biological benefits of CR without reducing actual food intake can be considered CR mimetics, whether functional, pharmaceutical, nutraceutical, or other. Some of the best known candidates include resveratrol and related agents, the antidiabetic drug metformin, and rapamycin and other mTOR regulators. While the mechanisms of action vary, these and essentially all CR mimetic candidates work through at least some of the same pathways as actual CR. While the entire field continues to evolve rapidly, the current status will be reviewed here, with particular focus on recent developments, the most practical relevance and applicability for potential consumers, and new strategies for the future.

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Oncotarget. 2015 May 30;6(15):12909-19.

Energy excess is the main cause of accelerated aging of mammals.

Biliński T[1], Paszkiewicz T[2], Zadrag-Tecza R[1].

Author information

Abstract

The analysis of cases of unusually high longevity of naked mole rats and an alternative explanation of the phenomenon of calorie restriction effects in monkeys allowed for postulating that any factor preventing an excess of energy consumed, leads to increased lifespan, both in evolutionary and an individual lifetime scale. It is postulated that in mammals the most destructive processes resulting in shortening of life are not restricted to the phenomena explained by the hyperfunction theory of Mikhail Blagosklonny. Hyperfunction, understood as unnecessary or even adverse syntheses of cell components, can be to some extent prevented by lowered intake of nutrients when body growth ceases. We postulate also the contribution of glyco/lipotoxicity to aging, resulting from the excess of energy. Besides two other factors seem to participate in aging. One of them is lack of telomerase activity in some somatic cells. The second factor concerns epigenetic phenomena. Excessive activity of epigenetic maintenance system probably turns off some crucial organismal functions. Another epigenetic factor playing important role could be the micro RNA system deciding on expression of numerous age-related diseases. However, low extrinsic mortality from predation is a conditio sine qua non of the expression of all longevity phenotypes in animals. Among all long-lived animals, naked mole rats are unique in the elimination of neoplasia, which is accompanied by delayed functional symptoms of senescence. The question whether simultaneous disappearance of neoplasia and delayed senescence is accidental or not remains open.

Curr Opin Cell Biol. 2015 Jun 12;34:75-83. doi: 10.1016/j.ceb.2015.05.007. [Epub ahead of print]

DNA repair defects and genome instability in Hutchinson-Gilford Progeria Syndrome.

Gonzalo S[1], Kreienkamp R[2].

Author information

Abstract

The integrity of the nuclear lamina has emerged as an important factor in the maintenance of genome stability. In particular, mutations in the LMNA gene, encoding A-type lamins (lamin A/C), alter nuclear morphology and function, and cause genomic instability. LMNA gene mutations are associated with a variety of degenerative diseases and devastating premature aging syndromes such as Hutchinson-Gilford Progeria Syndrome (HGPS) and Restrictive Dermopathy (RD). HGPS is a severe laminopathy, with patients dying in their teens from myocardial infarction or stroke. HGPS patient-derived cells exhibit nuclear shape abnormalities, changes in epigenetic regulation and gene expression, telomere shortening, genome instability, and premature senescence. This review highlights recent advances in identifying molecular mechanisms that contribute to the pathophysiology of HGPS, with a special emphasis on DNA repair defects and genome instability.

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Compr Physiol. 2015 Jul 1;5(3):1069-121. doi: 10.1002/cphy.c140063.

Cardiac Physiology of Aging: Extracellular Considerations.

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Author information

Abstract

Aging is a major risk factor for the development of cardiovascular disease, with the majority of affected patients being elderly. Progressive changes to myocardial structure and function occur with aging, often in concert with underlying pathologies. However, whether chronological aging results in a remodeled "aged substrate" has yet to be established. In addition to myocyte contractility, myocardial performance relies heavily on the cardiac extracellular matrix (ECM), the roles of which are as dynamic as they are significant; including providing structural integrity, assisting in force transmission throughout the cardiac cycle and acting as a signaling medium for communication between cells and the extracellular environment. In the healthy heart, ECM homeostasis must be maintained, and matrix deposition is in balance with degradation. Consequently, alterations to, or misregulation of the cardiac ECM has been shown to occur in both aging and in pathological remodeling with disease. Mounting evidence suggests that age-induced matrix remodeling may occur at the level of ECM control; including collagen synthesis, deposition, maturation, and degradation. Furthermore, experimental studies using aged animal models not only suggest that the aged heart may respond differently to insult than the young, but the identification of key players specific to remodeling with age may hold future therapeutic potential for the treatment of cardiac dysfunction in the elderly. This review will focus on the role of the cardiac interstitium in the physiology of the aging myocardium, with particular emphasis on the implications to age-related remodeling in disease. © 2015 American Physiological Society. Compr Physiol 5:1069-1121, 2015.

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Redox Biol. 2015 Jul 3;6:51-72. doi: 10.1016/j.redox.2015.06.019. [Epub ahead of print]

Redox regulation of FoxO transcription factors.

Klotz LO[1], Sánchez-Ramos C[2], Prieto-Arroyo I[2], Urbánek P[3], Steinbrenner H[3], Monsalve M[4].

⊕ Author information

Abstract

Transcription factors of the forkhead box, class O (FoxO) family are important regulators of the cellular stress response and promote the cellular antioxidant defense. On one hand, FoxOs stimulate the transcription of genes coding for antioxidant proteins located in different subcellular compartments, such as in mitochondria (i.e. superoxide dismutase-2, peroxiredoxins 3 and 5) and peroxisomes (catalase), as well as for antioxidant proteins found extracellularly in plasma (e.g., selenoprotein P and ceruloplasmin). On the other hand, reactive oxygen species (ROS) as well as other stressful stimuli that elicit the formation of ROS, may modulate FoxO activity at multiple levels, including posttranslational modifications of FoxOs (such as phosphorylation and acetylation), interaction with coregulators, alterations in FoxO subcellular localization, protein synthesis and stability. Moreover, transcriptional and posttranscriptional control of the expression of genes coding for FoxOs is sensitive to ROS. Here, we review these aspects of FoxO biology focusing on redox regulation of FoxO signaling, and with emphasis on the interplay between ROS and FoxOs under various physiological and pathophysiological conditions. Of particular interest are the dual role played by FoxOs in cancer development and their key role in whole body nutrient homeostasis, modulating metabolic adaptations and/or disturbances in response to low vs. high nutrient intake. Examples discussed here include calorie restriction and starvation as well as adipogenesis, obesity and type 2 diabetes.

Long noncoding RNAs in cardiac development and ageing

A large part of the mammalian genome is transcribed into noncoding RNAs. Long noncoding RNAs (lncRNAs) have emerged as critical epigenetic regulators of gene expression. Distinct molecular mechanisms allow lncRNAs either to activate or to repress gene expression, thereby participating in the regulation of cellular and tissue function. LncRNAs, therefore, have important roles in healthy and diseased hearts, and might be targets for therapeutic intervention. In this Review, we summarize the current knowledge of the roles of lncRNAs in cardiac development and ageing. After describing the definition and classification of lncRNAs, we present an overview of the mechanisms by which lncRNAs regulate gene expression. We discuss the multiple roles of lncRNAs in the heart, and focus on the regulation of embryonic stem cell differentiation, cardiac cell fate and development, and cardiac ageing. We emphasize the importance of chromatin remodelling in this regulation. Finally, we discuss the therapeutic and biomarker potential of lncRNAs.

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Adiposity and cancer risk: new mechanistic insights from epidemiology

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Abstract

Abstract • References • Author information • Supplementary information

Excess body adiposity, commonly expressed as body mass index (BMI), is a risk factor for many common adult cancers. Over the past decade, epidemiological data have shown that adiposity–cancer risk associations are specific for gender, site, geographical population, histological subtype and molecular phenotype. The biological mechanisms underpinning these associations are incompletely understood but need to take account of the specificities observed in epidemiology to better inform future prevention strategies.

Int J Epidemiol. 2015 Apr;44(2):578-86. doi: 10.1093/ije/dyv094. Epub 2015 May 27.

Adiposity as a cause of cardiovascular disease: a Mendelian randomization study.

Hägg S[1], Fall T[1], Ploner A[1], Mägi R[1], Fischer K[1], Draisma HH[1], Kals M[1], de Vries PS[1], Dehghan A[1], Willems SM[1], Sarin AP[1], Kristiansson K[1], Nuotio ML[1], Havulinna AS[1], de Bruijn RF[1], Ikram MA[1], Kuningas M[1], Stricker BH[1], Franco OH[1], Benyamin B[1], Gieger C[1], Hall AS[1], Huikari V[1], Jula A[1], Järvelin MR[1], Kaakinen M[1], Kaprio J[1], Kobl M[1], Mangino M[1], Nelson CP[1], Palotie A[1], Samani NJ[1], Spector TD[1], Strachan DP[1], Tobin MD[1], Whitfield JB[1], Uitterlinden AG[1], Salomaa V[1], Syvänen AC[1], Kuulasmaa K[1], Magnusson PK[1], Esko T[1], Hofman A[1], de Geus EJ[1], Lind L[1], Giedraitis V[1], Perola M[1], Evans A[1], Ferrières J[1], Virtamo J[1], Kee F[1], Tregouet DA[1], Arveiler D[1], Amouyel P[1], Gianfagna F[1], Brambilla P[1], Ripatti S[1], van Duijn CM[1], Metspalu A[1], Prokopenko I[1], McCarthy MI[1], Pedersen NL[1], Ingelsson E[1]; European Network for Genetic and Genomic Epidemiology (ENGAGE) consortium.

⊕ Author information

Abstract

BACKGROUND: Adiposity, as indicated by body mass index (BMI), has been associated with risk of cardiovascular diseases in epidemiological studies. We aimed to investigate if these associations are causal, using Mendelian randomization (MR) methods.

METHODS: The associations of BMI with cardiovascular outcomes [coronary heart disease (CHD), heart failure and ischaemic stroke], and associations of a genetic score (32 BMI single nucleotide polymorphisms) with BMI and cardiovascular outcomes were examined in up to 22 193 individuals with 3062 incident cardiovascular events from nine prospective follow-up studies within the ENGAGE consortium. We used random-effects meta-analysis in an MR framework to provide causal estimates of the effect of adiposity on cardiovascular outcomes.

RESULTS: There was a strong association between BMI and incident CHD (HR = 1.20 per SD-increase of BMI, 95% CI, 1.12-1.28, P = 1.9·10(-7)), heart failure (HR = 1.47, 95% CI, 1.35-1.60, P = 9·10(-19)) and ischaemic stroke (HR = 1.15, 95% CI, 1.06-1.24, P = 0.0008) in observational analyses. The genetic score was robustly associated with BMI (β = 0.030 SD-increase of BMI per additional allele, 95% CI, 0.028-0.033, P = 3·10(-107)). Analyses indicated a causal effect of adiposity on development of heart failure (HR = 1.93 per SD-increase of BMI, 95% CI, 1.12-3.30, P = 0.017) and ischaemic stroke (HR = 1.83, 95% CI, 1.05-3.20, P = 0.034). Additional cross-sectional analyses using both ENGAGE and CARDIoGRAMplusC4D data showed a causal effect of adiposity on CHD.

CONCLUSIONS: Using MR methods, we provide support for the hypothesis that adiposity causes CHD, heart failure and, previously not demonstrated, ischaemic stroke.

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Layers of structure and function in protein aggregation

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Protein aggregation is a central hallmark of many neurodegenerative disorders, but the relationship of aggregate structural diversity to the resultant cellular cytotoxicity and phenotypic diversity has remained obscure. Recent advances in understanding the mechanisms of protein aggregation and their physiological consequences have been achieved through chemical biology approaches, such as rationally designed protein modifications and chemical probes, providing crucial mechanistic insights and promise for therapeutic strategies for brain disorders.