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Scientific News
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Sven Bulterijs

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Health and Human Services Secretary Tom Price at today's House of Representatives hearing.

MICHAEL REYNOLDS/EPA/Newscom

Trump wants 2018 NIH cut to come from overhead payments

By Jocelyn Kaiser | Mar. 29, 2017 , 4:15 PM

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Trump's NIH budget may include reducing overhead payments to universities

By Jocelyn Kaiser | Mar. 17, 2017 , 5:00 PM

In general, universities that are awarded an NIH grant for the direct costs of a research project can receive from 10% to 100% of that amount to cover indirect costs. In fiscal year 2016, NIH paid out $6.4 billion for indirect costs in addition to the $16.9 billion in direct costs for research projects and other awards it funded.

Indirect costs have long been controversial. Investigators often see the payments as a tax that reduces the size of their research grants. And some policy experts say that universities **have too much leeway to use the money for things such as fancy new buildings**. Meanwhile, many private foundations pay much lower overhead rates—for example, the **Bill & Melinda Gates Foundation limits indirect costs to 10% for U.S. universities**.

Sign Victor’s petition on Change.org

Klassificera åldrandet som en sjukdom i Sverige

Victor Björk Uppsala, Sweden

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Novartis offloads phase 2 mTORC1 programs to PureTech

by *Nick Paul Taylor* | Mar 24, 2017 4:24am

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The DrugAge database of aging-related drugs

Aging is a major worldwide medical challenge. Not surprisingly, identifying drugs and compounds that extend lifespan in model organisms is a growing research area. Here, we present DrugAge (http://genomics.senescence.info/drugs/), a curated database of lifespan-extending drugs and compounds. At the time of writing, DrugAge contains 1316 entries featuring 418 different compounds from studies across 27 model organisms, including worms, flies, yeast and mice. Data were manually curated from 324 publications. Using drug–gene interaction data, we also performed a functional enrichment analysis of targets of lifespan-extending drugs. Enriched terms include various functional categories related to glutathione and antioxidant activity, ion transport and metabolic processes. In addition, we found a modest but significant overlap between targets of lifespan-extending drugs and known aging-related genes, suggesting that some but not most aging-related pathways have been targeted pharmacologically in longevity studies. DrugAge is freely available online for the scientific community and will be an important resource for biogerontologists.

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Targeted Apoptosis of Senescent Cells Restores Tissue Homeostasis in Response to Chemotoxicity and Aging

The accumulation of irreparable cellular damage restricts healthspan after acute stress or natural aging. Senescent cells are thought to impair tissue function, and their genetic clearance can delay features of aging. Identifying how senescent cells avoid apoptosis allows for the prospective design of anti-senescence compounds to address whether homeostasis can also be restored. Here, we identify FOXO4 as a pivot in senescent cell viability. We designed a FOXO4 peptide that perturbs the FOXO4 interaction with p53. In senescent cells, this selectively causes p53 nuclear exclusion and cell-intrinsic apoptosis. Under conditions where it was well tolerated in vivo, this FOXO4 peptide neutralized doxorubicin-induced chemotoxicity. Moreover, it restored fitness, fur density, and renal function in both fast aging $Xpd^{TTD/TTD}$ and naturally aged mice. Thus, therapeutic targeting of senescent cells is feasible under conditions where loss of health has already occurred, and in doing so tissue homeostasis can effectively be restored.

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A conserved NAD^+ binding pocket that regulates protein-protein interactions during aging

Abstract

DNA repair is essential for life, yet its efficiency declines with age for reasons that are unclear. Numerous proteins possess Nudix homology domains (NHDs) that have no known function. We show that NHDs are NAD^+ (oxidized form of nicotinamide adenine dinucleotide) binding domains that regulate protein-protein interactions. The binding of NAD^+ to the NHD domain of DBC1 (deleted in breast cancer 1) prevents it from inhibiting PARP1 [poly(adenosine diphosphate–ribose) polymerase], a critical DNA repair protein. As mice age and NAD^+ concentrations decline, DBC1 is increasingly bound to PARP1, causing DNA damage to accumulate, a process rapidly reversed by restoring the abundance of NAD^+. Thus, NAD^+ directly regulates protein-protein interactions, the modulation of which may protect against cancer, radiation, and aging.

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Nicotinamide Ameliorates Disease Phenotypes in a Human iPSC Model of Age-Related Macular Degeneration

Age-related macular degeneration (AMD) affects the retinal pigment epithelium (RPE), a cell monolayer essential for photoreceptor survival, and is the leading cause of vision loss in the elderly. There are no disease-altering therapies for dry AMD, which is characterized by accumulation of subretinal drusen deposits and complement-driven inflammation. We report the derivation of human-induced pluripotent stem cells (hiPSCs) from patients with diagnosed AMD, including two donors with the rare *ARMS2/HTRA1* homozygous genotype. The hiPSC-derived RPE cells produce several AMD/drusen-related proteins, and those from the AMD donors show significantly increased complement and inflammatory factors, which are most exaggerated in the ARMS2/HTRA1 lines. Using a panel of AMD biomarkers and candidate drug screening, combined with transcriptome analysis, we discover that nicotinamide (NAM) ameliorated disease-related phenotypes by inhibiting drusen proteins and inflammatory and complement factors while upregulating nucleosome, ribosome, and chromatin-modifying genes. Thus, targeting NAM-regulated pathways is a promising avenue for developing therapeutics to combat AMD.

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Stem cell divisions, somatic mutations, cancer etiology, and cancer prevention

Abstract

Cancers are caused by mutations that may be inherited, induced by environmental factors, or result from DNA replication errors (R). We studied the relationship between the number of normal stem cell divisions and the risk of 17 cancer types in 69 countries throughout the world. The data revealed a strong correlation (median = 0.80) between cancer incidence and normal stem cell divisions in all countries, regardless of their environment. The major role of R mutations in cancer etiology was supported by an independent approach, based solely on cancer genome sequencing and epidemiological data, which suggested that R mutations are responsible for two-thirds of the mutations in human cancers. All of these results are consistent with epidemiological estimates of the fraction of cancers that can be prevented by changes in the environment. Moreover, they accentuate the importance of early detection and intervention to reduce deaths from the many cancers arising from unavoidable R mutations.

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Fasting-Mimicking Diet Promotes Ngn3-Driven β-Cell Regeneration to Reverse Diabetes

Stem-cell-based therapies can potentially reverse organ dysfunction and diseases, but the removal of impaired tissue and activation of a program leading to organ regeneration pose major challenges. In mice, a 4-day fasting mimicking diet (FMD) induces a stepwise expression of Sox17 and Pdx-1, followed by Ngn3-driven generation of insulin-producing β cells, resembling that observed during pancreatic development. FMD cycles restore insulin secretion and glucose homeostasis in both type 2 and type 1 diabetes mouse models. In human type 1 diabetes pancreatic islets, fasting conditions reduce PKA and mTOR activity and induce Sox2 and Ngn3 expression and insulin production. The effects of the FMD are reversed by IGF-1 treatment and recapitulated by PKA and mTOR inhibition. These results indicate that a FMD promotes the reprogramming of pancreatic cells to restore insulin generation in islets from T1D patients and reverse both T1D and T2D phenotypes in mouse models.

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Sci Transl Med. 2017 Feb 15;9(377). pii: eaai8700. doi: 10.1126/scitranslmed.aai8700.

Fasting-mimicking diet and markers/risk factors for aging, diabetes, cancer, and cardiovascular disease.

Wei M[1], Brandhorst S[1], Shelehchi M[1], Mirzaei H[1], Cheng CW[1], Budniak J[1], Groshen S[2], Mack WJ[2], Guen E[1], Di Biase S[1], Cohen P[1], Morgan TE[1], Dorff T[3], Hong K[4], Michalsen A[5], Laviano A[6], Longo VD[7,8].

Author information

Abstract

Calorie restriction or changes in dietary composition can enhance healthy aging, but the inability of most subjects to adhere to chronic and extreme diets, as well as potentially adverse effects, limits their application. We randomized 100 generally healthy participants from the United States into two study arms and tested the effects of a fasting-mimicking diet (FMD)-low in calories, sugars, and protein but high in unsaturated fats-on markers/risk factors associated with aging and age-related diseases. We compared subjects who followed 3 months of an unrestricted diet to subjects who consumed the FMD for 5 consecutive days per month for 3 months. Three FMD cycles reduced body weight, trunk, and total body fat; lowered blood pressure; and decreased insulin-like growth factor 1 (IGF-1). No serious adverse effects were reported. After 3 months, control diet subjects were crossed over to the FMD program, resulting in a total of 71 subjects completing three FMD cycles. A post hoc analysis of subjects from both FMD arms showed that body mass index, blood pressure, fasting glucose, IGF-1, triglycerides, total and low-density lipoprotein cholesterol, and C-reactive protein were more beneficially affected in participants at risk for disease than in subjects who were not at risk. Thus, cycles of a 5-day FMD are safe, feasible, and effective in reducing markers/risk factors for aging and age-related diseases. Larger studies in patients with diagnosed diseases or selected on the basis of risk factors are warranted to confirm the effect of the FMD on disease prevention and treatment.

Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease

RESULTS

At 48 weeks, the least-squares mean percentage reduction in LDL cholesterol levels with evolocumab, as compared with placebo, was 59%, from a median baseline value of 92 mg per deciliter (2.4 mmol per liter) to 30 mg per deciliter (0.78 mmol per liter) ($P<0.001$). Relative to placebo, evolocumab treatment significantly reduced the risk of the primary end point (1344 patients [9.8%] vs. 1563 patients [11.3%]; hazard ratio, 0.85; 95% confidence interval [CI], 0.79 to 0.92; $P<0.001$) and the key secondary end point (816 [5.9%] vs. 1013 [7.4%]; hazard ratio, 0.80; 95% CI, 0.73 to 0.88; $P<0.001$). The results were consistent across key subgroups, including the subgroup of patients in the lowest quartile for baseline LDL cholesterol levels (median, 74 mg per deciliter [1.9 mmol per liter]). There was no significant difference between the study groups with regard to adverse events (including new-onset diabetes and neurocognitive events), with the exception of injection-site reactions, which were more common with evolocumab (2.1% vs. 1.6%).

Full Text of Results...

CONCLUSIONS

In our trial, inhibition of PCSK9 with evolocumab on a background of statin therapy lowered LDL cholesterol levels to a median of 30 mg per deciliter (0.78 mmol per liter) and reduced the risk of cardiovascular events. These findings show that patients with atherosclerotic cardiovascular disease benefit from lowering of LDL cholesterol levels below current targets. (Funded by Amgen; FOURIER ClinicalTrials.gov number, NCT01764633.)

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Association Between Dietary Factors and Mortality From Heart Disease, Stroke, and Type 2 Diabetes in the United States

Key Points

Question What is the estimated mortality due to heart disease, stroke, or type 2 diabetes (cardiometabolic deaths) associated with suboptimal intakes of 10 dietary factors in the United States?

Findings In 2012, suboptimal intake of dietary factors was associated with an estimated 318 656 cardiometabolic deaths, representing 45.4% of cardiometabolic deaths. The highest proportions of cardiometabolic deaths were estimated to be related to excess sodium intake, insufficient intake of nuts/seeds, high intake of processed meats, and low intake of seafood omega-3 fats.

Meaning Suboptimal intake of specific foods and nutrients was associated with a substantial proportion of deaths due to heart disease, stroke, or type 2 diabetes.

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53BP1 contributes to regulation of autophagic clearance of mitochondria.

Youn CK[1,2], Kim HB[1,2], Wu TT[1,3], Park S[4], Cho SI[5], Lee JH[1,3].

⊕ Author information

Abstract

Autophagy, the primary recycling pathway within cells, plays a critical role in mitochondrial quality control under normal growth conditions and in the cellular response to stress. Here we provide evidence that 53BP1, a DNA damage response protein, is involved in regulating mitochondrial clearance from the cell via a type of autophagy termed mitophagy. We found that when either human or mouse cells were 53BP1-deficient, there was an increase in mitochondrial abnormalities, as observed through staining intensity, aggregation, and increased mass. Moreover, a 53BP1-depleted cell population included an increased number of cells with a high mitochondrial membrane potential (ΔΨm) relative to controls, suggesting that the loss of 53BP1 prevents initiation of mitophagy thereby leading to the accumulation of damaged mitochondria. Indeed, both 53BP1 and the mitophagy-associated protein LC3 translocated to mitochondria in response to damage induced by the mitochondrial uncoupler carbonyl cyanide m-chlorophenylhydrazone (CCCP). The recruitment of parkin, an E3-ubiquitin ligase, to mitochondria in response to CCCP treatment was significantly decreased in 53BP1-deficient cells. And lastly, using p53-deficient H1299 cells, we confirmed that the role of 53BP1 in mitophagy is independent of p53. These data support a model in which 53BP1 plays an important role in modulating mitochondrial homeostasis and in the clearance of damaged mitochondria.

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Lifespan differences between queens and workers are not explained by rates of molecular damage

The biological processes that underlie senescence are of universal biological importance, yet they remain poorly understood. A popular theory proposes that senescence is the result of limited investment into mechanisms involved in the prevention and repair of molecular damage, leading to an accumulation of molecular damage with age. In ants, queen and worker lifespans differ by an order of magnitude, and this remarkable difference in lifespan has been shown to be associated with differences in the expression of genes involved in DNA and protein repair. Here we use the comet assay and Western Blotting for poly-ubiquitinated proteins to explore whether these differences in expression lead to differences in the accumulation of DNA damage (comet assay) or protein damage (protein ubiquitination) with age. Surprisingly, there was no difference between queens and workers in the rate of accumulation of DNA damage. We also found that levels of ubiquitinated proteins decreased with age, as previously reported in honeybees. This is in contrast to what has been found in model organisms such as worms and flies. Overall, these results reveal that the link between investment into macromolecular repair, age-related damage accumulation and lifespan is more complex than usually recognised.

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Regulation of Life Span by the Gut Microbiota in The Short-Lived African Turquoise Killifish

Gut bacteria occupy the interface between the organism and the external environment, contributing to homeostasis and disease. Yet, the causal role of the gut microbiota during host aging is largely unexplored. Here, using the African turquoise killifish (*Nothobranchius furzeri*), a naturally short-lived vertebrate, we show that the gut microbiota plays a key role in modulating vertebrate life span. Recolonizing the gut of middle-age individuals with bacteria from young donors resulted in life span extension and delayed behavioral decline. This intervention prevented the decrease in microbial diversity associated with host aging and maintained a young-like gut bacterial community, characterized by overrepresentation of the key genera *Exiguobacterium*, *Planococcus*, *Propionigenium* and *Psychrobacter*. Our findings demonstrate that the natural microbial gut community of young individuals can causally induce long-lasting beneficial systemic effects that lead to life span extension in a vertebrate model.

Residual Cdk1/2 activity after DNA damage promotes senescence

In response to DNA damage, a cell can be forced to permanently exit the cell cycle and become senescent. Senescence provides an early barrier against tumor development by preventing proliferation of cells with damaged DNA. By studying single cells, we show that Cdk activity persists after DNA damage until terminal cell cycle exit. This low level of Cdk activity not only allows cell cycle progression, but also promotes cell cycle exit at a decision point in G2 phase. We find that residual Cdk1/2 activity is required for efficient p21 production, allowing for nuclear sequestration of Cyclin B1, subsequent APC/C^{Cdh1}-dependent degradation of mitotic inducers and induction of senescence. We suggest that the same activity that triggers mitosis in an unperturbed cell cycle enforces senescence in the presence of DNA damage, ensuring a robust response when most needed.

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Increased genome instability is not accompanied by sensitivity to DNA damaging agents in aged yeast cells

The budding yeast *Saccharomyces cerevisiae* divides asymmetrically, producing a new daughter cell from the original mother cell. While daughter cells are born with a full lifespan, a mother cell ages with each cell division and can only generate on average 25 daughter cells before dying. Aged yeast cells exhibit genomic instability, which is also a hallmark of human aging. However, it is unclear how this genomic instability contributes to aging. To shed light on this issue, we investigated endogenous DNA damage in *S. cerevisiae* during replicative aging and tested for age-dependent sensitivity to exogenous DNA damaging agents. Using live-cell imaging in a microfluidic device, we show that aging yeast cells display an increase in spontaneous Rad52 foci, a marker of endogenous DNA damage. Strikingly, this elevated DNA damage is not accompanied by increased sensitivity of aged yeast cells to genotoxic agents nor by global changes in the proteome or transcriptome that would indicate a specific "DNA damage signature". These results indicate that DNA repair proficiency is not compromised in aged yeast cells, suggesting that yeast replicative aging and age-associated genomic instability is likely not a consequence of an inability to repair DNA damage.

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DNA methylation signatures in peripheral blood strongly predict all-cause mortality

DNA methylation (DNAm) has been revealed to play a role in various diseases. Here we performed epigenome-wide screening and validation to identify mortality-related DNAm signatures in a general population-based cohort with up to 14 years follow-up. In the discovery panel in a case-cohort approach, 11,063 CpGs reach genome-wide significance (FDR<0.05). 58 CpGs, mapping to 38 well-known disease-related genes and 14 intergenic regions, are confirmed in a validation panel. A mortality risk score based on ten selected CpGs exhibits strong association with all-cause mortality, showing hazard ratios (95% CI) of 2.16 (1.10–4.24), 3.42 (1.81–6.46) and 7.36 (3.69–14.68), respectively, for participants with scores of 1, 2–5 and 5+ compared with a score of 0. These associations are confirmed in an independent cohort and are independent from the 'epigenetic clock'. In conclusion, DNAm of multiple disease-related genes are strongly linked to mortality outcomes. The DNAm-based risk score might be informative for risk assessment and stratification.

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Impact of Dietary Interventions on Noncoding RNA Networks and mRNAs Encoding Chromatin-Related Factors

Dietary interventions dramatically affect metabolic disease and lifespan in various aging models. Here, we profiled liver microRNA (miRNA), coding, and long non-coding RNA (lncRNA) expression by high-throughput deep sequencing in mice across multiple energy intake and expenditure interventions. Strikingly, three dietary intervention network design patterns were uncovered: (1) lifespan-extending interventions largely repressed the expression of miRNAs, lncRNAs, and transposable elements; (2) protein-coding mRNAs with expression positively correlated with long lifespan are highly targeted by miRNAs; and (3) miRNA-targeting interactions mainly target chromatin-related functions. We experimentally validated miR-34a, miR-107, and miR-212-3p targeting of the chromatin remodeler *Chd1* and further demonstrate that *Chd1* knockdown mimics high-fat diet and aging-induced gene expression changes and activation of transposons. Our findings demonstrate lifespan-extending diets repress miRNA-chromatin remodeler interactions and safeguard against deregulated transcription induced by aging and lifespan shortening diets, events linked by microRNA, chromatin, and ncRNA crosstalk.

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Enhanced Protein Translation Underlies Improved Metabolic and Physical Adaptations to Different Exercise Training Modes in Young and Old

The molecular transducers of benefits from different exercise modalities remain incompletely defined. Here we report that 12 weeks of high-intensity aerobic interval (HIIT), resistance (RT), and combined exercise training enhanced insulin sensitivity and lean mass, but only HIIT and combined training improved aerobic capacity and skeletal muscle mitochondrial respiration. HIIT revealed a more robust increase in gene transcripts than other exercise modalities, particularly in older adults, although little overlap with corresponding individual protein abundance was noted. HIIT reversed many age-related differences in the proteome, particularly of mitochondrial proteins in concert with increased mitochondrial protein synthesis. Both RT and HIIT enhanced proteins involved in translational machinery irrespective of age. Only small changes of methylation of DNA promoter regions were observed. We provide evidence for predominant exercise regulation at the translational level, enhancing translational capacity and proteome abundance to explain phenotypic gains in muscle mitochondrial function and hypertrophy in all ages.

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Physiological frailty index (PFI): quantitative in-life estimate of individual biological age in mice

The development of healthspan-extending pharmaceuticals requires quantitative estimation of age-related progressive physiological decline. In humans, individual health status can be quantitatively assessed by means of a *frailty index* (FI), a parameter which reflects the scale of accumulation of age-related deficits. However, adaptation of this methodology to animal models is a challenging task since it includes multiple subjective parameters. Here we report a development of a quantitative non-invasive procedure to estimate biological age of an individual animal by creating *physiological frailty index* (PFI). We demonstrated the dynamics of PFI increase during chronological aging of male and female NIH Swiss mice. We also demonstrated acceleration of growth of PFI in animals placed on a high fat diet, reflecting aging acceleration by obesity and provide a tool for its quantitative assessment. Additionally, we showed that PFI could reveal anti-aging effect of mTOR inhibitor rapatar (bioavailable formulation of rapamycin) prior to registration of its effects on longevity. PFI revealed substantial sex-related differences in normal chronological aging and in the efficacy of detrimental (high fat diet) or beneficial (rapatar) aging modulatory factors. Together, these data introduce PFI as a reliable, non-invasive, quantitative tool suitable for testing potential anti-aging pharmaceuticals in pre-clinical studies.

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MicroRNAs miR-203-3p, miR-664-3p and miR-708-5p are associated with median strain lifespan in mice.

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Author information

Abstract

MicroRNAs (miRNAs) are small non-coding RNA species that have been shown to have roles in multiple processes that occur in higher eukaryotes. They act by binding to specific sequences in the 3' untranslated region of their target genes and causing the transcripts to be degraded by the RNA-induced silencing complex (RISC). MicroRNAs have previously been reported to demonstrate altered expression in several aging phenotypes such as cellular senescence and age itself. Here, we have measured the expression levels of 521 small regulatory microRNAs (miRNAs) in spleen tissue from young and old animals of 6 mouse strains with different median strain lifespans by quantitative real-time PCR. Expression levels of 3 microRNAs were robustly associated with strain lifespan, after correction for multiple statistical testing (miR-203-3p [β-coefficient = -0.6447, $p = 4.8 \times 10^{-11}$], miR-664-3p [β-coefficient = 0.5552, $p = 5.1 \times 10^{-8}$] and miR-708-5p [β-coefficient = 0.4986, $p = 1.6 \times 10^{-6}$]). Pathway analysis of binding sites for these three microRNAs revealed enrichment of target genes involved in key aging and longevity pathways including mTOR, FOXO and MAPK, most of which also demonstrated associations with longevity. Our results suggests that miR-203-3p, miR-664-3p and miR-708-5p may be implicated in pathways determining lifespan in mammals.

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Insulin-like growth factor 1 deficiency exacerbates hypertension-induced cerebral microhemorrhages in mice, mimicking the aging phenotype

Clinical and experimental studies show that aging exacerbates hypertension-induced cerebral microhemorrhages (CMHs), which progressively impair neuronal function. There is growing evidence that aging promotes insulin-like growth factor 1 (IGF-1) deficiency, which compromises multiple aspects of cerebromicrovascular and brain health. To determine the role of IGF-1 deficiency in the pathogenesis of CMHs, we induced hypertension in mice with liver-specific knockdown of IGF-1 (*Igf1*$^{f/f}$ + TBG-Cre-AAV8) and control mice by angiotensin II plus L-NAME treatment. In IGF-1-deficient mice, the same level of hypertension led to significantly earlier onset and increased incidence and neurological consequences of CMHs, as compared to control mice, as shown by neurological examination, gait analysis, and histological assessment of CMHs in serial brain sections. Previous studies showed that in aging, increased oxidative stress-mediated matrix metalloprotease (MMP) activation importantly contributes to the pathogenesis of CMHs. Thus, it is significant that hypertension-induced cerebrovascular oxidative stress and MMP activation were increased in IGF-1-deficient mice. We found that IGF-1 deficiency impaired hypertension-induced adaptive media hypertrophy and extracellular matrix remodeling, which together with the increased MMP activation likely also contributes to increased fragility of intracerebral arterioles. Collectively, IGF-1 deficiency promotes the pathogenesis of CMHs, mimicking the aging phenotype, which likely contribute to its deleterious effect on cognitive function. Therapeutic strategies that upregulate IGF-1 signaling in the cerebral vessels and/or reduce microvascular oxidative stress, and MMP activation may be useful for the prevention of CMHs, protecting cognitive function in high-risk elderly patients.

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Dietary restriction improves repopulation but impairs lymphoid differentiation capacity of hematopoietic stem cells in early aging

Dietary restriction (DR) improves health, delays tissue aging, and elongates survival in flies and worms. However, studies on laboratory mice and nonhuman primates revealed ambiguous effects of DR on lifespan despite improvements in health parameters. In this study, we analyzed consequences of adult-onset DR (24 h to 1 yr) on hematopoietic stem cell (HSC) function. DR ameliorated HSC aging phenotypes, such as the increase in number of HSCs and the skewing toward myeloid-biased HSCs during aging. Furthermore, DR increased HSC quiescence and improved the maintenance of the repopulation capacity of HSCs during aging. In contrast to these beneficial effects, DR strongly impaired HSC differentiation into lymphoid lineages and particularly inhibited the proliferation of lymphoid progenitors, resulting in decreased production of peripheral B lymphocytes and impaired immune function. The study shows that DR-dependent suppression of growth factors and interleukins mediates these divergent effects caused by DR. Supplementation of insulin-like growth factor 1 partially reverted the DR-induced quiescence of HSCs, whereas IL-6/IL-7 substitutions rescued the impairment of B lymphopoiesis exposed to DR. Together, these findings delineate positive and negative effects of long-term DR on HSC functionality involving distinct stress and growth signaling pathways.

REVIEWS/COMMENTS/EDITORIALS

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mTOR Signaling in Growth, Metabolism, and Disease

The mechanistic target of rapamycin (mTOR) coordinates eukaryotic cell growth and metabolism with environmental inputs, including nutrients and growth factors. Extensive research over the past two decades has established a central role for mTOR in regulating many fundamental cell processes, from protein synthesis to autophagy, and deregulated mTOR signaling is implicated in the progression of cancer and diabetes, as well as the aging process. Here, we review recent advances in our understanding of mTOR function, regulation, and importance in mammalian physiology. We also highlight how the mTOR signaling network contributes to human disease and discuss the current and future prospects for therapeutically targeting mTOR in the clinic.

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J Bras Nefrol. 2017 Mar;39(1):59-64. doi: 10.5935/0101-2800.20170010.

When kidneys get old: an essay on nephro-geriatrics.

[Article in English, Portuguese]

Glassock R[1], Denic A[2], Rule AD[2].

Author information

Abstract

Aging is a nearly universal phenomenon in biology only partially controlled by genetic endowment. Individuals and their organs age at varying rates. The kidneys manifest the aging process by steady loss of nephrons and a corresponding decrease in glomerular filtration rate (GFR) beginning about age 30 years. The mechanisms responsible for this observation is are elusive. However, defining chronic kidney disease based on arbitrary, fixed thresholds of GFR in the later phases of life can be problematical as it may over-diagnosis CKD in the elderly. A modest, persisting reduction of GFR (around 45-59 ml/min/1.73m2) without abnormal proteinuria does not seem to confer much of an adverse effect on mortality and remaining life expectancy in older adults and the development of end-stage renal disease in such subjects is very uncommon. Old kidneys should not be equated with "diseased" kidneys.

Arterial ageing: from endothelial dysfunction to vascular calcification

Complex structural and functional changes occur in the arterial system with advancing age. The aged artery is characterized by changes in microRNA expression patterns, autophagy, smooth muscle cell migration and proliferation, and arterial calcification with progressively increased mechanical vessel rigidity and stiffness. With age the vascular smooth muscle cells modify their phenotype from contractile to 'synthetic' determining the development of intimal thickening as early as the second decade of life as an adaptive response to forces acting on the arterial wall. The increased permeability observed in intimal thickening could represent the substrate on which low-level atherosclerotic stimuli can promote the development of advanced atherosclerotic lesions. In elderly patients the atherosclerotic plaques tend to be larger with increased vascular stenosis. In these plaques there is a progressive accumulation of both lipids and collagen and a decrease of inflammation. Similarly the plaques from elderly patients show more calcification as compared with those from younger patients. The coronary artery calcium score is a well-established marker of adverse cardiovascular outcomes. The presence of diffuse calcification in a severely stenotic segment probably induces changes in mechanical properties and shear stress of the arterial wall favouring the rupture of a vulnerable lesion in a less stenotic adjacent segment. Oxidative stress and inflammation appear to be the two primary pathological mechanisms of ageing-related endothelial dysfunction even in the absence of clinical disease. Arterial ageing is no longer considered an inexorable process. Only a better understanding of the link between ageing and vascular dysfunction can lead to significant advances in both preventative and therapeutic treatments with the aim that in the future vascular ageing may be halted or even reversed.

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Amyloid beta modulators and neuroprotection in Alzheimer's disease: a critical appraisal

Multiple cellular changes have been identified as being involved in Alzheimer's disease (AD) pathogenesis, including mitochondrial damage, synaptic loss, amyloid beta (Aβ) production and/or accumulation, inflammatory responses, and phosphorylated tau formation and/or accumulation. Studies have established that Aβ-induced synaptic dysfunction is dependent on abnormal amyloid precursor protein (APP) processing caused by β- and γ-secretases, resulting in the generation of Aβ. The Aβ formed as a result of abnormal APP processing induces phosphorylated tau and activates glycogen synthase kinase-3β (GSK3β) and cyclin-dependent kinase-5 (CDK5). Here, we review the latest research on the development of Aβ modulators for neuroprotection in AD. We also review the use of molecular inhibitors as therapeutic targets in AD.

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Centenarians as extreme phenotypes: An ecological perspective to get insight into the relationship between the genetics of longevity and age-associated diseases

In this review, we address the genetic *continuum* between aging and age-related diseases, with particular attention to the ecological perspective. We describe the connections between genes that promote longevity and genes associated with age-related diseases considering tradeoff mechanisms in which the same genetic variants could have different effects according to the tissue considered and could be involved in several biological pathways. Then we describe mechanisms of antagonistic pleiotropy, focusing on the complex interplay between genetic variants and environmental changes (internal or external). We sustain the use of centenarians as "super-controls" for the study of the major age-related diseases, starting from the concept that the maximization of the phenotypic differences in the considered cohort, achieved by selecting the most divergent phenotypes, could be useful for increasing the significant differences observed in the genetic association study. We describe the potential impact of the population genetic variability in the study of human longevity and the possible contribution of the past selective pressures in shaping the current genomic background of individuals. In conclusion, we illustrate recent findings emerged from whole-genome sequencing of long-lived individuals and future perspectives for interpreting the huge amount of genetic data that will be generated in the next future.

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The role of dietary carbohydrates in organismal aging

Carbohydrates are essential nutrients that are used as a primary source of energy. Carbohydrate utilization should be properly controlled, as abnormal regulation of carbohydrate metabolism is associated with diseases, such as diabetes, cardiovascular diseases, and stroke. These metabolic syndromes have become a serious problem in developed countries, and there is an increased need for research examining the influence of carbohydrates on animal physiology. Diets enriched in glucose, a major carbohydrate, are also associated with accelerated aging in several model organisms, including yeast and *Caenorhabditis elegans* (*C. elegans*). Genetic factors that mediate the effects of high glucose diets on aging have been identified during the last decade, mostly through the use of *C. elegans*. In this review, we describe studies that determine the effects of carbohydrate-enriched diets on aging by focusing on the mechanisms through which evolutionarily conserved pathways mediate the lifespan-altering effects of glucose in *C. elegans*. These include the insulin/insulin-like growth factor-1, sterol-regulatory element-binding protein, and AMP-activated protein kinase signaling pathways. We also discuss the effects of various carbohydrates and carbohydrate-derived metabolites on aging in model organisms and cultured mammalian cells. Finally, we discuss how dietary carbohydrates influence health and aging in humans.

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The Fountain of Youth by Targeting Senescent Cells?

The potential to reverse aging has long been a tantalizing thought, but has equally been considered mere utopia. Recently, the spotlights have turned to senescent cells as being a culprit for aging. Can these cells be therapeutically eliminated? When so? And is this even safe? Recent developments in the tool box to study senescence have made it possible to begin addressing these questions. It will be especially relevant to identify how senescence impairs tissue rejuvenation and to prospectively design compounds that can both target senescence and stimulate rejuvenation in a safe manner. This review argues that to fulfill this niche, cell-penetrating peptides may provide promising therapeutics. As a candidate approach, the author also highlights the potential of targeting individual FOXO signaling pathways to combat senescence and stimulate tissue rejuventaion.

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