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Health & Science

Fueled by drug crisis, U.S. life expectancy declines for a second straight year

By **Lenny Bernstein** and **Christopher Ingraham** December 21, 2017 

American life expectancy at birth declined for the second consecutive year in 2016, fueled by a staggering 21 percent rise in the death rate from drug overdoses, the Centers for Disease Control and Prevention reported Thursday.

The United States has not seen two years of declining life expectancy since 1962 and 1963, when influenza caused an inordinate number of deaths. In 1993, there was a one-year drop during the worst of the AIDS epidemic.

“I think we should take it very seriously,” said Bob Anderson, chief of the Mortality Statistics Branch at the National Center for Health Statistics, which is part of the CDC. “If you look at the other developed countries in the world, they’re not seeing this kind of thing. Life expectancy is going up.”

The development is a dismal sign for the United States, which boasts some of the world’s highest spending on medical care, and more evidence of the toll the nation’s opioid crisis is exacting on younger and middle-aged Americans, experts said.

Pharmacologic Interventions to Prevent Cognitive Decline, Mild Cognitive Impairment, and Clinical Alzheimer-Type Dementia: A Systematic Review

Data Synthesis: Fifty-one unique trials were rated as having low to moderate risk of bias (including 3 that studied dementia medications, 16 antihypertensives, 4 diabetes medications, 2 nonsteroidal anti-inflammatory drugs [NSAIDs] or aspirin, 17 hormones, and 7 lipid-lowering agents). In persons with normal cognition, estrogen and estrogen–progestin increased risk for dementia or a combined outcome of MCI or dementia (1 trial, low strength of evidence); high-dose raloxifene decreased risk for MCI but not for dementia (1 trial, low strength of evidence); and antihypertensives (4 trials), NSAIDs (1 trial), and statins (1 trial) did not alter dementia risk (low to insufficient strength of evidence). In persons with MCI, cholinesterase inhibitors did not reduce dementia risk (1 trial, low strength of evidence). In persons with normal cognition and those with MCI, these pharmacologic treatments neither improved nor slowed decline in cognitive test performance (low to insufficient strength of evidence). Adverse events were inconsistently reported but were increased for estrogen (stroke), estrogen–progestin (stroke, coronary heart disease, invasive breast cancer, and pulmonary embolism), and raloxifene (venous thromboembolism).

Limitation: High attrition, short follow-up, inconsistent cognitive outcomes, and possible selective reporting and publication.

Conclusion: Evidence does not support use of the studied pharmacologic treatments for cognitive protection in persons with normal cognition or MCI.

Data Synthesis: Of 11 trials with low or medium risk of bias, 6 enrolled healthy adults with normal cognition and 5 enrolled adults with MCI. Trainings for healthy older adults were mostly computer based; those for adults with MCI were mostly held in group sessions. The MCI trials used attention controls more often than trials with healthy populations. For healthy older adults, training improved cognitive performance in the domain trained but not in other domains (moderate-strength evidence). Results for populations with MCI suggested no effect of training on performance (low-strength and insufficient evidence). Evidence for prevention of cognitive decline or dementia was insufficient. Adverse events were not reported.

Limitation: Heterogeneous interventions and outcome measures; outcomes that mostly assessed test performance rather than global function or dementia diagnosis; potential publication bias.

Conclusion: In older adults with normal cognition, training improves cognitive performance in the domain trained. Evidence regarding prevention or delay of cognitive decline or dementia is insufficient.

Physical Activity Interventions in Preventing Cognitive Decline and Alzheimer-Type Dementia: A Systematic Review

Data Synthesis: Of 32 eligible trials, 16 with low to moderate risk of bias compared a physical activity intervention with an inactive control. Most trials had 6-month follow-up; a few had 1- or 2-year follow-up. Evidence was insufficient to draw conclusions about the effectiveness of aerobic training, resistance training, or tai chi for improving cognition. Low-strength evidence showed that multicomponent physical activity interventions had no effect on cognitive function. Low-strength evidence showed that a multidomain intervention comprising physical activity, diet, and cognitive training improved several cognitive outcomes. Evidence regarding effects on dementia prevention was insufficient for all physical activity interventions.

Limitation: Heterogeneous interventions and cognitive test measures, small and underpowered studies, and inability to assess the clinical significance of cognitive test outcomes.

Conclusion: Evidence that short-term, single-component physical activity interventions promote cognitive function and prevent cognitive decline or dementia in older adults is largely insufficient. A multidomain intervention showed a delay in cognitive decline (low-strength evidence).

Over-the-Counter Supplement Interventions to Prevent Cognitive Decline, Mild Cognitive Impairment, and Clinical Alzheimer-Type Dementia: A Systematic Review

Data Synthesis: Thirty-eight trials with low to medium risk of bias compared ω -3 fatty acids, soy, ginkgo biloba, B vitamins, vitamin D plus calcium, vitamin C or β -carotene, multi-ingredient supplements, or other OTC interventions with placebo or other supplements. Few studies examined effects on clinical Alzheimer-type dementia or MCI, and those that did suggested no benefit. Daily folic acid plus vitamin B₁₂ was associated with improvements in performance on some objectively measured memory tests that were statistically significant but of questionable clinical significance. Moderate-strength evidence showed that vitamin E had no benefit on cognition. Evidence about effects of ω -3 fatty acids, soy, ginkgo biloba, folic acid alone or with other B vitamins, β -carotene, vitamin C, vitamin D plus calcium, and multivitamins or multi-ingredient supplements was either insufficient or low-strength, suggesting that these supplements did not reduce risk for cognitive decline. Adverse events were rarely reported.

Limitation: Studies had high attrition and short follow-up and used a highly variable set of cognitive outcome measures.

Conclusion: Evidence is insufficient to recommend any OTC supplement for cognitive protection in adults with normal cognition or MCI.

Microglia-derived ASC specks cross-seed amyloid- β in Alzheimer's disease

The spreading of pathology within and between brain areas is a hallmark of neurodegenerative disorders. In patients with Alzheimer's disease, deposition of amyloid- β is accompanied by activation of the innate immune system and involves inflammasome-dependent formation of ASC specks in microglia. ASC specks released by microglia bind rapidly to amyloid- β and increase the formation of amyloid- β oligomers and aggregates, acting as an inflammation-driven cross-seed for amyloid- β pathology. Here we show that intrahippocampal injection of ASC specks resulted in spreading of amyloid- β pathology in transgenic double-mutant $APP_{Swe}PSEN1_{dE9}$ mice. By contrast, homogenates from brains of $APP_{Swe}PSEN1_{dE9}$ mice failed to induce seeding and spreading of amyloid- β pathology in ASC-deficient $APP_{Swe}PSEN1_{dE9}$ mice. Moreover, co-application of an anti-ASC antibody blocked the increase in amyloid- β pathology in $APP_{Swe}PSEN1_{dE9}$ mice. These findings support the concept that inflammasome activation is connected to seeding and spreading of amyloid- β pathology in patients with Alzheimer's disease.

Defective cholesterol clearance limits remyelination in the aged central nervous system

Abstract

Age-associated decline in regeneration capacity limits the restoration of nervous system functionality after injury. In a model for demyelination, we found that old mice fail to resolve the inflammatory response initiated after myelin damage. Aged phagocytes accumulated excessive amounts of myelin debris, which triggered cholesterol crystal formation, phagolysosomal membrane rupture, and stimulated inflammasomes. Myelin debris clearance required cholesterol transporters including apolipoprotein E. Remarkably, stimulation of reverse cholesterol transport was sufficient to restore the capacity of old mice to remyelinate lesioned tissue. Thus, cholesterol-rich myelin debris can overwhelm the efflux capacity of phagocytes, resulting in a phase transition of cholesterol into crystals thereby inducing a maladaptive immune response that impedes tissue regeneration.

Reducing the RNA binding protein TIA1 protects against tau-mediated neurodegeneration in vivo

Daniel J. Apicco, Peter E. A. Ash, [...] Benjamin Wolozin 

Emerging studies suggest a role for tau in regulating the biology of RNA binding proteins (RBPs). We now show that reducing the RBP T-cell intracellular antigen 1 (TIA1) in vivo protects against neurodegeneration and prolongs survival in transgenic P301S Tau mice. Biochemical fractionation shows co-enrichment and co-localization of tau oligomers and RBPs in transgenic P301S Tau mice. Reducing TIA1 decreased the number and size of granules co-localizing with stress granule markers. Decreasing TIA1 also inhibited the accumulation of tau oligomers at the expense of increasing neurofibrillary tangles. Despite the increase in neurofibrillary tangles, TIA1 reduction increased neuronal survival and rescued behavioral deficits and lifespan. These data provide in vivo evidence that TIA1 plays a key role in mediating toxicity and further suggest that RBPs direct the pathway of tau aggregation and the resulting neurodegeneration. We propose a model in which dysfunction of the translational stress response leads to tau-mediated pathology.

Tau-mediated iron export prevents ferroptotic damage after ischemic stroke

Functional failure of tau contributes to age-dependent, iron-mediated neurotoxicity, and as iron accumulates in ischemic stroke tissue, we hypothesized that tau failure may exaggerate ischemia-reperfusion-related toxicity. Indeed, unilateral, transient middle cerebral artery occlusion (MCAO) suppressed hemispheric tau and increased iron levels in young (3-month-old) mice and rats. Wild-type mice were protected by iron-targeted interventions: ceruloplasmin and amyloid precursor protein ectodomain, as well as ferroptosis inhibitors. At this age, tau-knockout mice did not express elevated brain iron and were protected against hemispheric reperfusion injury following MCAO, indicating that tau suppression may prevent ferroptosis. However, the accelerated age-dependent brain iron accumulation that occurs in tau-knockout mice at 12 months of age negated the protective benefit of tau suppression against MCAO-induced focal cerebral ischemia-reperfusion injury. The protective benefit of tau knockout was revived in older mice by iron-targeting interventions. These findings introduce tau-iron interaction as a pleiotropic modulator of ferroptosis and ischemic stroke outcome.

Raman spectroscopy imaging reveals interplay between atherosclerosis and medial calcification in the human aorta

Abstract

Medial calcification in the human aorta accumulates during aging and is known to be aggravated in several diseases. Atherosclerosis, another major cause of cardiovascular calcification, shares some common aggravators. However, the mechanisms of cardiovascular calcification remain poorly understood. To elucidate the relationship between medial aortic calcification and atherosclerosis, we characterized the cross-sectional distributions of the predominant minerals in aortic tissue, apatite and whitlockite, and the associated extracellular matrix. We also compared the cellular changes between atherosclerotic and nonatherosclerotic human aortic tissues. This was achieved through the development of Raman spectroscopy imaging methods that adapted algorithms to distinguish between the major biomolecules present within these tissues. We present a relationship between apatite, cholesterol, and triglyceride in atherosclerosis, with the relative amount of all molecules concurrently increased in the atherosclerotic plaque. Further, the increase in apatite was disproportionately large in relation to whitlockite in the aortic media directly underlying a plaque, indicating that apatite is more pathologically significant in atherosclerosis-aggravated medial calcification. We also discovered a reduction of β -carotene in the whole aortic intima, including a plaque in atherosclerotic aortic tissues compared to nonatherosclerotic tissues. This unprecedented biomolecular characterization of the aortic tissue furthers our understanding of pathological and physiological cardiovascular calcification events in humans.

Biochem Biophys Res Commun. 2018 Jan 1;495(1):1122-1128. doi: 10.1016/j.bbrc.2017.11.144. Epub 2017 Nov 22.

Role of pyroptosis in normal cardiac response to calorie restriction and starvation.

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⊕ Author information

Abstract

AIMS: An unhealthy diet is a major risk factor for cardiac diseases. Most researches focus on high fat diet, little is known about the detrimental effects of starvation on heart.

METHODS: Mice were fed 100%, 40% and 20% of ad libitum to mimic the situation of moderate and severe caloric restriction (CR). To further evaluate the different effect of CR and starvation on cardiomyocyte, AC16 cells were treated with different concentrations of serum or glucose. TUNEL staining was performed to evaluate DNA damage in AC16 cells. HE and Masson staining were performed to detect the morphology and degree of fibrosis in myocardium from mice. Immunohistochemical staining, immunofluorescence staining, western blot and real-time PCR were used to detect the protein and mRNA expression of caspase-1, IL-1 β and IL-18.

RESULTS: CR and starvation decrease body weight of mice in a concentration dependent manner. The starvation group showed a remarkable myocardial fibrosis with no significant alteration between control and CR groups. CR inhibited the activation of caspase-1 as well as the expression of IL-1 β and IL-18. On the contrary, starvation plays completely opposite effects, which was in accordance with histological changes. Similarly, different levels of serum and glucose deprivation were used to mimic the effect of CR and starvation in vitro. Moderate level of serum and glucose deprivation exerts protective effect on AC16 cells through the inhibition of pyroptosis, whereas high level of serum and glucose deprivation induces cell injury through the induction of pyroptosis.

CONCLUSION: CR alleviates pyroptosis, whereas starvation promotes the progression of pyroptosis in myocardial tissues and cells.

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Senescence promotes in vivo reprogramming through p16^{INK4a} and IL-6

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Summary

Cellular senescence is a damage response aimed to orchestrate tissue repair. We have recently reported that cellular senescence, through the paracrine release of interleukin-6 (IL6) and other soluble factors, strongly favors cellular reprogramming by Oct4, Sox2, Klf4, and c-Myc (OSKM) in non-senescent cells. Indeed, activation of OSKM in mouse tissues triggers senescence in some cells and reprogramming in other cells, both processes occurring concomitantly and in close proximity. In this system, *Ink4a/Arf*-null tissues cannot undergo senescence, fail to produce IL6, and cannot reprogram efficiently; whereas *p53*-null tissues undergo extensive damage and senescence, produce high levels of IL6, and reprogram efficiently. Here, we have further explored the genetic determinants of in vivo reprogramming. We report that *Ink4a*, but not *Arf*, is necessary for OSKM-induced senescence and, thereby, for the paracrine stimulation of reprogramming. However, in the absence of *p53*, IL6 production and reprogramming become independent of *Ink4a*, as revealed by the analysis of *Ink4a/Arf/p53* deficient mice. In the case of the cell cycle inhibitor p21, its protein levels are highly elevated upon OSKM activation in a p53-independent manner, and we show that *p21*-null tissues present increased levels of senescence, IL6, and reprogramming. We also report that *Il6*-mutant tissues are impaired in undergoing reprogramming, thus reinforcing the critical role of IL6 in reprogramming. Finally, young female mice present lower efficiency of in vivo reprogramming compared to male mice, and this gender difference disappears with aging, both observations being consistent with the known anti-inflammatory effect of estrogens. The current findings regarding the interplay between senescence and reprogramming may conceivably apply to other contexts of tissue damage.

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A network-based meta-analysis for characterizing the genetic landscape of human aging.

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Abstract

Great amounts of omics data are generated in aging research, but their diverse and partly complementary nature requires integrative analysis approaches for investigating aging processes and connections to age-related diseases. To establish a broader picture of the genetic and epigenetic landscape of human aging we performed a large-scale meta-analysis of 6600 human genes by combining 35 datasets that cover aging hallmarks, longevity, changes in DNA methylation and gene expression, and different age-related diseases. To identify biological relationships between aging-associated genes we incorporated them into a protein interaction network and characterized their network neighborhoods. In particular, we computed a comprehensive landscape of more than 1000 human aging clusters, network regions where genes are highly connected and where gene products commonly participate in similar processes. In addition to clusters that capture known aging processes such as nutrient-sensing and mTOR signaling, we present a number of clusters with a putative functional role in linking different aging processes as promising candidates for follow-up studies. To enable their detailed exploration, all datasets and aging clusters are made freely available via an interactive website (<https://gemex.eurac.edu/bioinf/age/>).

Abstract

We undertook a genome-wide association study (GWAS) of parental longevity in European descent UK Biobank participants. For combined mothers' and fathers' attained age, 10 loci were associated ($p < 5 \times 10^{-8}$), including 8 previously identified for traits including survival, Alzheimer's and cardiovascular disease. Of these, 4 were also associated with longest 10% survival (mothers age ≥ 90 years, fathers ≥ 87 years), with 2 additional associations including *MC2R* intronic variants (coding for the adrenocorticotrophic hormone receptor). Mother's age at death was associated with 3 additional loci (2 linked to autoimmune conditions), and 8 for fathers only. An attained age genetic risk score associated with parental survival in the US Health and Retirement Study and the Wisconsin Longitudinal Study and with having a centenarian parent ($n=1,181$) in UK Biobank. The results suggest that human longevity is highly polygenic with prominent roles for loci likely involved in cellular senescence and inflammation, plus lipid metabolism and cardiovascular conditions. There may also be gender specific routes to longevity.

Abstract

Chronic low grade inflammation is a fundamental mechanism of aging. We estimated biologic age using nine biomarkers from diverse inflammatory pathways and we hypothesized that genes associated with inflammatory biological age would provide insights into human aging. In Framingham Offspring Study participants at examination 8 (2005 to 2008), we used the Klemera-Doubal method to estimate inflammatory biologic age and we computed the difference (Δ Age) between biologic age and chronologic age. Gene expression in whole blood was measured using the Affymetrix Human Exon 1.0 ST Array. We used linear mixed effect models to test associations between inflammatory Δ Age and gene expression (dependent variable) adjusting for age, sex, imputed cell counts, and technical covariates. Our study sample included 2386 participants (mean age $67A \pm 9$ years, 55% women). There were 448 genes significantly were associated with inflammatory Δ Age ($P < 2.8 \times 10^{-6}$), 302 genes were positively associated and 146 genes were negatively associated. Pathway analysis among the identified genes highlighted the NOD-like receptor signaling and ubiquitin mediated proteolysis pathways. In summary, we identified 448 genes that were significantly associated with inflammatory biologic age. Future functional characterization may identify molecular interventions to delay aging and prolong healthspan in older adults.

Abstract

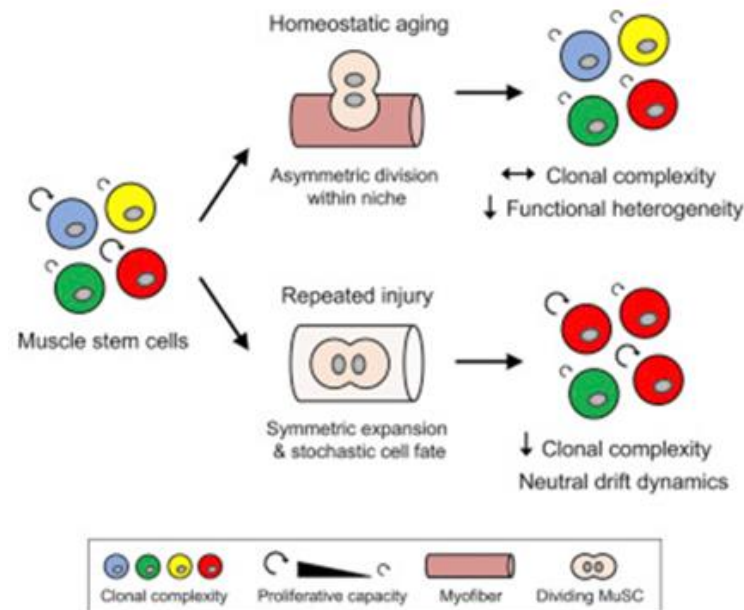
Over 30 million cancer survivors exist worldwide. Survivors have an earlier onset and higher incidence of chronic comorbidities, including endocrinopathies, cardiac dysfunction, osteoporosis, pulmonary fibrosis, secondary cancers and frailty than the general population; however, the fundamental basis of these changes at the cellular level is unknown. An electronic search was performed on Embase, Medline In-Process & Other Non-Indexed Citations, and the Cochrane Central Register of Controlled Trials. Original articles addressing the cellular biology of ageing and/or the mechanisms of cancer therapies similar to ageing mechanisms were included, and references of these articles were reviewed for further search. We found multiple biological processes of ageing at the cellular level and their association with cancer therapies, as well as with clinical effects. The direct effects of various chemotherapies and radiation on telomere length, senescent cells, epigenetic modifications and microRNA were found. We review the effects of cancer therapies on recognised hallmarks of ageing. Long-term comorbidities seen in cancer survivors mimic the phenotypes of ageing and likely result from the interaction between therapeutic exposures and the underlying biology of ageing. Long-term follow-up of cancer survivors and research on prevention strategies should be pursued to increase the length and quality of life among the growing population of cancer survivors.

Restoration of metabolic health by decreased consumption of branched-chain amino acids

Obesity and diabetes are increasing problems around the world, and although even moderate weight loss can improve metabolic health, reduced calorie diets are notoriously difficult to sustain. Branched-chain amino acids (BCAAs; leucine, isoleucine and valine) are elevated in the blood of obese, insulin-resistant humans and rodents. We recently demonstrated that specifically reducing dietary levels of BCAAs has beneficial effects on the metabolic health of young, growing mice, improving glucose tolerance and modestly slowing fat mass gain. In the present study, we examine the hypothesis that reducing dietary BCAAs will promote weight loss, reduce adiposity, and improve blood glucose control in diet-induced obese mice with pre-existing metabolic syndrome. We find that specifically reducing dietary BCAAs rapidly reverses diet-induced obesity and improves glucoregulatory control in diet-induced obese mice. Most dramatically, mice eating an otherwise unhealthy high-calorie, high-sugar Western diet with reduced levels of BCAAs lost weight and fat mass rapidly until regaining a normal weight. Importantly, this normalization of weight was mediated not by caloric restriction or increased activity, but by increased energy expenditure, and was accompanied by a transient induction of the energy balance regulating hormone FGF21 (fibroblast growth factor 21). Consumption of a Western diet reduced in BCAAs was also accompanied by a dramatic improvement in glucose tolerance and insulin resistance. Our results link dietary BCAAs with the regulation of metabolic health and energy balance in obese animals, and suggest that specifically reducing dietary BCAAs may represent a highly translatable option for the treatment of obesity and insulin resistance.

Summary

The clonal complexity of adult stem cell pools is progressively lost during homeostatic turnover in several tissues, suggesting a decrease in the number of stem cells with distinct clonal origins. The functional impact of reduced complexity on stem cell pools, and how different tissue microenvironments may contribute to such a reduction, are poorly understood. Here, we performed clonal multicolor lineage tracing of skeletal muscle stem cells (MuSCs) to address these questions. We found that MuSC clonal complexity is maintained during aging despite heterogeneous reductions in proliferative capacity, allowing aged muscle to mount a clonally diverse, albeit diminished, response to injury. In contrast, repeated bouts of tissue repair cause a progressive reduction in MuSC clonal complexity indicative of neutral drift. Consistently, biostatistical modeling suggests that MuSCs undergo symmetric expansions with stochastic fate acquisition during tissue repair. These findings establish distinct principles that underlie stem cell dynamics during homeostatic aging and muscle regeneration.



REVIEWS/COMMENTS/EDITORIALS

The twilight of immunity: emerging concepts in aging of the immune system

Janko Nikolich-Žugich 

Immunosenescence is a series of age-related changes that affect the immune system and, with time, lead to increased vulnerability to infectious diseases. This Review addresses recent developments in the understanding of age-related changes that affect key components of immunity, including the effect of aging on cells of the (mostly adaptive) immune system, on soluble molecules that guide the maintenance and function of the immune system and on lymphoid organs that coordinate both the maintenance of lymphocytes and the initiation of immune responses. I further address the effect of the metagenome and exposome as key modifiers of immune-system aging and discuss a conceptual framework in which age-related changes in immunity might also affect the basic rules by which the immune system operates.

Fighting against a protean enemy: immunosenescence, vaccines, and healthy aging

The progressive increase of the aged population worldwide mandates new strategies to ensure sustained health and well-being with age. The development of better and/or new vaccines against pathogens that affect older adults is one pivotal intervention in approaching this goal. However, the functional decline of various physiological systems, including the immune system, requires novel approaches to counteract immunosenescence. Although important progress has been made in understanding the mechanisms underlying the age-related decline of the immune response to infections and vaccinations, knowledge gaps remain, both in the areas of basic and translational research. In particular, it will be important to better understand how environmental factors, such as diet, physical activity, co-morbidities, and pharmacological treatments, delay or contribute to the decline of the capability of the aging immune system to appropriately respond to infectious diseases and vaccination. Recent findings suggest that successful approaches specifically targeted to the older population can be developed, such as the high-dose and adjuvanted vaccines against seasonal influenza, the adjuvanted subunit vaccine against herpes zoster, as well as experimental interventions with immune-potentiators or immunostimulants. Learning from these first successes may pave the way to developing novel and improved vaccines for the older adults and immunocompromised. With an integrated, holistic vaccination strategy, society will offer the opportunity for an improved quality of life to the segment of the population that is going to increase most significantly in numbers and proportion over future decades.

Amyloid- β and tau complexity – towards improved biomarkers and targeted therapies

Most neurodegenerative diseases are proteinopathies, which are characterized by the aggregation of misfolded proteins. Although many proteins have an intrinsic propensity to aggregate, particularly when cellular clearance systems start to fail in the context of ageing, only a few form fibrillar aggregates. In Alzheimer disease, the peptide amyloid- β (A β) and the protein tau aggregate to form plaques and tangles, respectively, which comprise the histopathological hallmarks of this disease. This Review discusses the complexity of A β biogenesis, trafficking, post-translational modifications and aggregation states. Tau and its various isoforms, which are subject to a vast array of post-translational modifications, are also explored. The methodological advances that revealed this complexity are described. Finally, the toxic effects of distinct species of tau and A β are discussed, as well as the concept of protein 'strains', and how this knowledge can facilitate the development of early disease biomarkers for stratifying patients and validating new therapies. By targeting distinct species of A β and tau for therapeutic intervention, the way might be paved for personalized medicine and more-targeted treatment strategies.

[Antioxid Redox Signal](#). 2017 Dec 28. doi: 10.1089/ars.2017.7479. [Epub ahead of print]

Signaling and regulation through the NAD⁺ and NADP⁺ networks.

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Abstract

SIGNIFICANCE: NAD⁺ and NADP⁺ are important co-substrates in redox reactions and participate in regulatory networks operating in adjustment of metabolic pathways. Moreover, NAD⁺ is a co-substrate in post-translational modification of proteins and is involved in DNA repair. NADPH is indispensable for reductive syntheses and the redox chemistry involved in attaining and maintaining correct protein conformation. Recent Advances: Within a pair of decades, a wealth of information has been gathered on NAD(H)⁺/NADP(H) redox imaging, regulatory role of redox potential in assembly of spatial protein structures and the role of ADP-ribosylation of regulatory proteins affecting both gene expression and metabolism. All this as a bearing also on disease, healthy ageing and longevity.

CRITICAL ISSUES: Knowledge of the signal propagation paths of NAD⁺-dependent post-translational modifications is still fragmentary for explaining the mechanism of cellular stress effects and nutritional state on these actions. Evaluation of the co-substrate and regulator roles of NAD(H) and NADP(H) still suffers from some controversies in experimental data.

FUTURE DIRECTIONS: Activating or inhibiting interventions in NAD⁺-dependent protein modifications for medical purposes have shown promise, but restraining tumor growth by inhibiting DNA repair in tumors by means of interference in sirtuins is still in early stage. The same is true for the use of this technology in improving health and healthy ageing. New genetically encoded specific NAD and NADP probes are expected to modernize the research on redox biology.

OTHER RESEARCH

Highlights

- A CRISPR/Cas9 system transcriptionally activates endogenous target genes *in vivo*
- Recruiting the transcriptional machinery induces *trans*-epigenetic remodeling
- Inducing target gene expression leads to physiological phenotypes in postnatal mammals
- The system ameliorates symptoms associated with several mouse models of human diseases

Summary

Current genome-editing systems generally rely on inducing DNA double-strand breaks (DSBs). This may limit their utility in clinical therapies, as unwanted mutations caused by DSBs can have deleterious effects. CRISPR/Cas9 system has recently been repurposed to enable target gene activation, allowing regulation of endogenous gene expression without creating DSBs. However, *in vivo* implementation of this gain-of-function system has proven difficult. Here, we report a robust system for *in vivo* activation of endogenous target genes through *trans*-epigenetic remodeling. The system relies on recruitment of Cas9 and transcriptional activation complexes to target loci by modified single guide RNAs. As proof-of-concept, we used this technology to treat mouse models of diabetes, muscular dystrophy, and acute kidney disease. Results demonstrate that CRISPR/Cas9-mediated target gene activation can be achieved *in vivo*, leading to measurable phenotypes and amelioration of disease symptoms. This establishes new avenues for developing targeted epigenetic therapies against human diseases.

