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Scientific News 6th of September 2015
Sven Bulterijs

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http://www.longevityreporter.org/

New crowdfunding platform for aging research

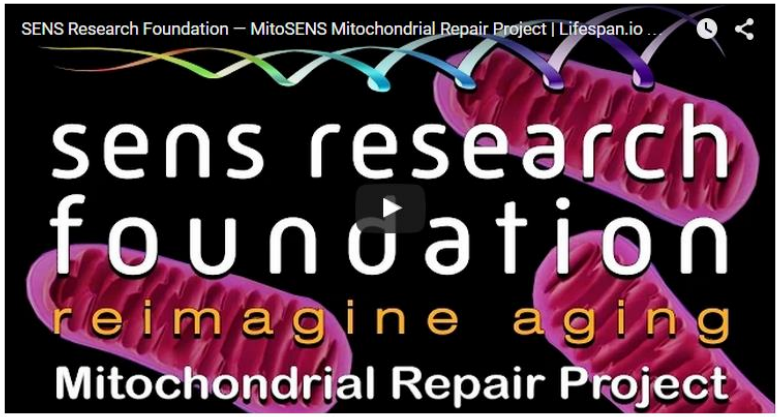
START BLOG PROJECTS lifespan.io HOW IT WORKS REGISTER LOGIN

MITOSENS MITOCHONDRIAL REPAIR PROJECT

Engineering backup copies of mitochondrial genes to place in the nucleus of the cell, aiming to prevent age-related damage and restore lost mitochondrial function.

BY DR. MATTHEW "OKI" O'CONNOR

COMMENTS BACKERS SEARCH



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International Statistical Classification of Diseases and Releated Health Problems (ICD-11)

World Health Organization

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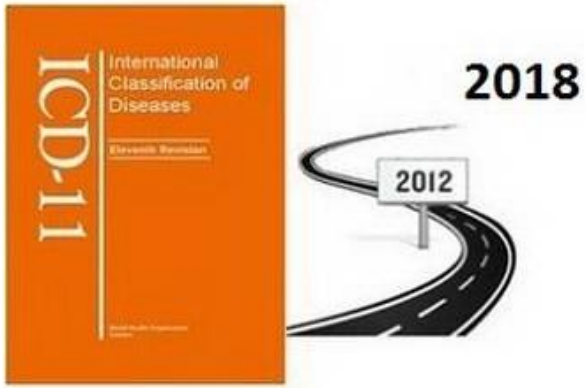
Classifications

- Family of International Classifications
- Family of International Classifications network
- Classification of Diseases (ICD)
- Classification of Functioning, Disability and Health (ICF)
- Classification of Health Interventions (ICHI)
- Frequently asked questions

The International Classification of Diseases 11th Revision is due by 2018



Participate in the ICD Revision

Beta phase participants will have the opportunity to:
- Make **Comments**
- Make **Proposals**
- Propose **definitions** of diseases in a structured way
- Participate in **Field Trials**
- Assist in **translating** ICD into other languages

Video invitation to participate

Frequently Asked Questions About ICD-11

ICD Information Sheet

ICD Revision Information Notes

ICD-11 Browser for browsing the classification and participating the development

http://www.who.int/classifications/icd/revision/en/

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Joined statement on genome editing from the Medical Research Council, the Academy of Medical Science, the Association of Medical Research Charities, the Biotechnology and Biological Sciences Research Council, and the Wellcome Trust

We must keep using CRISPR-Cas9 technology

by Guest Author on 2 September 2015

*Today we released a joint statement with other medical research funders in support of research using gene editing techniques such as CRISPR-Cas9 to advance our understanding of disease in preclinical research and to explore their potential for future therapeutic use. Here our Director of Science Programmes **Dr Rob Buckle** discusses the huge potential of gene editing, and why any attempt to use it in a therapeutic context must be the subject of the kind of intense and rigorous debate that the scientific community and UK regulatory system has demonstrated in the past.*

"Today's statement lays out our stance on the use of gene editing. We want research using CRISPR-Cas9 to continue, both as a tool for laboratory-based research and for the development of novel therapeutics, as highlighted above. This includes using the technique in pre-clinical research in human eggs, sperm and early embryos, so long as this is justified, scientifically and ethically, and within current UK law, where such research is strictly controlled."

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Global, regional, and national disability-adjusted life years (DALYs) for 306 diseases and injuries and healthy life expectancy (HALE) for 188 countries, 1990–2013: quantifying the epidemiological transition

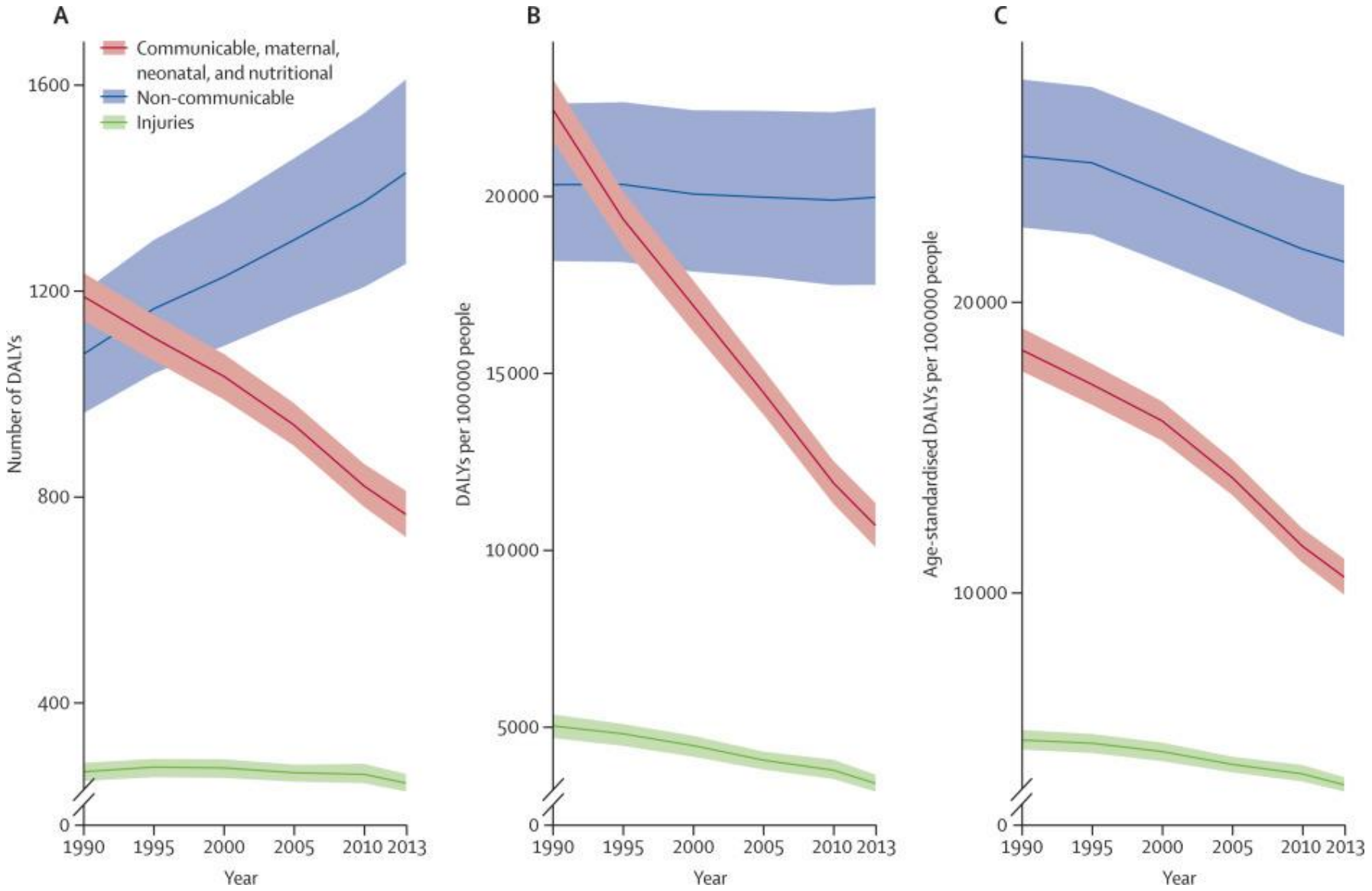
Findings

Worldwide, from 1990 to 2013, life expectancy at birth rose by 6·2 years (95% UI 5·6–6·6), from 65·3 years (65·0–65·6) in 1990 to 71·5 years (71·0–71·9) in 2013, HALE at birth rose by 5·4 years (4·9–5·8), from 56·9 years (54·5–59·1) to 62·3 years (59·7–64·8), total DALYs fell by 3·6% (0·3–7·4), and age-standardised DALY rates per 100 000 people fell by 26·7% (24·6–29·1). For communicable, maternal, neonatal, and nutritional disorders, global DALY numbers, crude rates, and age-standardised rates have all declined between 1990 and 2013, whereas for non–communicable diseases, global DALYs have been increasing, DALY rates have remained nearly constant, and age-standardised DALY rates declined during the same period. From 2005 to 2013, the number of DALYs increased for most specific non-communicable diseases, including cardiovascular diseases and neoplasms, in addition to dengue, food-borne trematodes, and leishmaniasis; DALYs decreased for nearly all other causes. By 2013, the five leading causes of DALYs were ischaemic heart disease, lower respiratory infections, cerebrovascular disease, low back and neck pain, and road injuries. Sociodemographic status explained more than 50% of the variance between countries and over time for diarrhoea, lower respiratory infections, and other common infectious diseases; maternal disorders; neonatal disorders; nutritional deficiencies; other communicable, maternal, neonatal, and nutritional diseases; musculoskeletal disorders; and other non-communicable diseases. However, sociodemographic status explained less than 10% of the variance in DALY rates for cardiovascular diseases; chronic respiratory diseases; cirrhosis; diabetes, urogenital, blood, and endocrine diseases; unintentional injuries; and self-harm and interpersonal violence. Predictably, increased sociodemographic status was associated with a shift in burden from YLLs to YLDs, driven by declines in YLLs and increases in YLDs from musculoskeletal disorders, neurological disorders, and mental and substance use disorders. In most country-specific estimates, the increase in life expectancy was greater than that in HALE. Leading causes of DALYs are highly variable across countries.

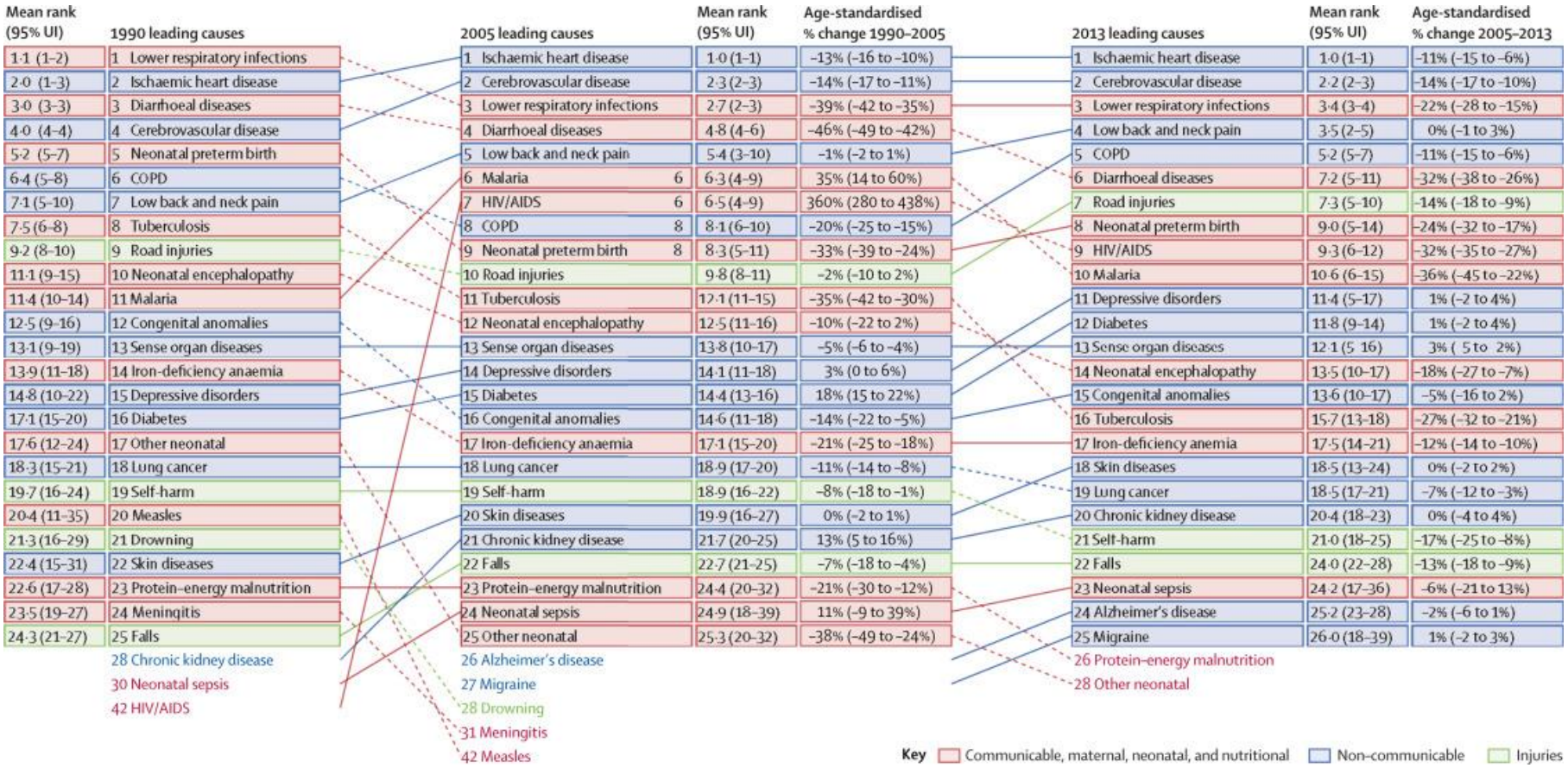
Interpretation

Global health is improving. Population growth and ageing have driven up numbers of DALYs, but crude rates have remained relatively constant, showing that progress in health does not mean fewer demands on health systems. The notion of an epidemiological transition—in which increasing sociodemographic status brings structured change in disease burden—is useful, but there is tremendous variation in burden of disease that is not associated with sociodemographic status. This further underscores the need for country-specific assessments of DALYs and HALE to appropriately inform health policy decisions and attendant actions.

From Lancet study…



From Lancet study…



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Autologous iPSC-derived dopamine neuron transplantation in a nonhuman primate Parkinson's disease model

Abstract

Abstract • Introduction • Results • Discussion • Materials and Methods • References • Acknowledgements • Author information • Supplementary information

Autologous dopamine (DA) neurons are a new cell source for replacement therapy of Parkinson's disease (PD). In this study, we tested the safety and efficacy of autologous induced pluripotent stem cell (iPSC)-derived DA cells for treatment of a cynomolgus monkey PD model. Monkey bone marrow mesenchymal cells were isolated and induced to iPSCs, followed by differentiation into DA cells using a method with high efficiency. Autologous DA cells were introduced into the brain of a cynomolgus monkey PD model without immunosuppression; three PD monkeys that had received no grafts served as controls. The PD monkey that had received autologous grafts experienced behavioral improvement compared with that of controls. Histological analysis revealed no overgrowth of grafts and a significant number of surviving A9 region-specific graft-derived DA neurons. The study provided a proof-of-principle to employ iPSC-derived autologous DA cells for PD treatment using a nonhuman primate PD model.

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Proc Natl Acad Sci U S A. 2015 Aug 24. pii: 201514844. [Epub ahead of print]

Effect of aging on muscle mitochondrial substrate utilization in humans.

Petersen KF[1], Morino K[2], Alves TC[1], Kibbey RG[1], Dufour S[3], Sono S[2], Yoo PS[4], Cline GW[1], Shulman GI[5].

Author information

Abstract

Previous studies have implicated age-associated reductions in mitochondrial oxidative phosphorylation activity in skeletal muscle as a predisposing factor for intramyocellular lipid (IMCL) accumulation and muscle insulin resistance (IR) in the elderly. To further investigate potential alterations in muscle mitochondrial function associated with aging, we assessed basal and insulin-stimulated rates of muscle pyruvate dehydrogenase (V_{PDH}) flux relative to citrate synthase flux (V_{CS}) in healthy lean, elderly subjects and healthy young body mass index- and activity-matched subjects. V_{PDH}/V_{CS} flux was assessed from the ^{13}C incorporation from of infused [1-^{13}C] glucose into glutamate [4-^{13}C] relative to alanine [3-^{13}C] assessed by LC-tandem MS in muscle biopsies. Insulin-stimulated rates of muscle glucose uptake were reduced by 25% ($P < 0.01$) in the elderly subjects and were associated with ~70% ($P < 0.04$) increase in IMCL, assessed by ^{1}H magnetic resonance spectroscopy. Basal V_{PDH}/V_{CS} fluxes were similar between the groups (young: 0.20 ± 0.03; elderly: 0.14 ± 0.03) and increased approximately threefold in the young subjects following insulin stimulation. However, this increase was severely blunted in the elderly subjects (young: 0.55 ± 0.04; elderly: 0.18 ± 0.02, $P = 0.0002$) and was associated with an ~40% ($P = 0.004$) reduction in insulin activation of Akt. These results provide new insights into acquired mitochondrial abnormalities associated with aging and demonstrate that age-associated reductions in muscle mitochondrial function and increased IMCL are associated with a marked inability of mitochondria to switch from lipid to glucose oxidation during insulin stimulation.

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Metabolic Damage and Premature Thymus Aging Caused by Stromal Catalase Deficiency

Summary

T lymphocytes are essential mediators of immunity that are produced by the thymus in proportion to its size. The thymus atrophies rapidly with age, resulting in progressive diminution of new T cell production. This decreased output is compensated by duplication of existing T cells, but it results in gradual dominance by memory T cells and decreased ability to respond to new pathogens or vaccines. Here, we show that accelerated and irreversible thymic atrophy results from stromal deficiency in the reducing enzyme catalase, leading to increased damage by hydrogen peroxide generated by aerobic metabolism. Genetic complementation of catalase in stromal cells diminished atrophy, as did chemical antioxidants, thus providing a mechanistic link between antioxidants, metabolism, and normal immune function. We propose that irreversible thymic atrophy represents a conventional aging process that is accelerated by stromal catalase deficiency in the context of an intensely anabolic (lymphoid) environment.

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Heterotypic Signals from Neural HSF-1 Separate Thermotolerance from Longevity

Summary

Integrating stress responses across tissues is essential for the survival of multicellular organisms. The metazoan nervous system can sense protein-misfolding stress arising in different subcellular compartments and initiate cytoprotective transcriptional responses in the periphery. Several subcellular compartments possess a homotypic signal whereby the respective compartment relies on a single signaling mechanism to convey information within the affected cell to the same stress-responsive pathway in peripheral tissues. In contrast, we find that the heat shock transcription factor, HSF-1, specifies its mode of transcellular protection via two distinct signaling pathways. Upon thermal stress, neural HSF-1 primes peripheral tissues through the thermosensory neural circuit to mount a heat shock response. Independent of this thermosensory circuit, neural HSF-1 activates the FOXO transcription factor, DAF-16, in the periphery and prolongs lifespan. Thus a single transcription factor can coordinate different stress response pathways to specify its mode of protection against changing environmental conditions.

Oocyte Factors Suppress Mitochondrial Polynucleotide Phosphorylase to Remodel the Metabolome and Enhance Reprogramming

Summary

Oocyte factors not only drive somatic cell nuclear transfer reprogramming but also augment the efficiency and quality of induced pluripotent stem cell (iPSC) reprogramming. Here, we show that the oocyte-enriched factors Tcl1 and Tcl1b1 significantly enhance reprogramming efficiency. Clonal analysis of pluripotency biomarkers further show that the Tcl1 oocyte factors improve the quality of reprogramming. Mechanistically, we find that the enhancement effect of Tcl1b1 depends on Akt, one of its putative targets. In contrast, Tcl1 suppresses the mitochondrial polynucleotide phosphorylase (PnPase) to promote reprogramming. Knockdown of PnPase rescues the inhibitory effect from *Tcl1* knockdown during reprogramming, whereas PnPase overexpression abrogates the enhancement from *Tcl1* overexpression. We further demonstrate that Tcl1 suppresses PnPase's mitochondrial localization to inhibit mitochondrial biogenesis and oxidation phosphorylation, thus remodeling the metabolome. Hence, we identified the Tcl1-PnPase pathway as a critical mitochondrial switch during reprogramming.

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Distinct Shifts in Microbiota Composition during *Drosophila* Aging Impair Intestinal Function and Drive Mortality

Summary

Alterations in the composition of the intestinal microbiota have been correlated with aging and measures of frailty in the elderly. However, the relationships between microbial dynamics, age-related changes in intestinal physiology, and organismal health remain poorly understood. Here, we show that dysbiosis of the intestinal microbiota, characterized by an expansion of the Gammaproteobacteria, is tightly linked to age-onset intestinal barrier dysfunction in *Drosophila*. Indeed, alterations in the microbiota precede and predict the onset of intestinal barrier dysfunction in aged flies. Changes in microbial composition occurring prior to intestinal barrier dysfunction contribute to changes in excretory function and immune gene activation in the aging intestine. In addition, we show that a distinct shift in microbiota composition follows intestinal barrier dysfunction, leading to systemic immune activation and organismal death. Our results indicate that alterations in microbiota dynamics could contribute to and also predict varying rates of health decline during aging in mammals.

Telomerase Is Essential for Zebrafish Heart Regeneration

Summary

After myocardial infarction in humans, lost cardiomyocytes are replaced by an irreversible fibrotic scar. In contrast, zebrafish hearts efficiently regenerate after injury. Complete regeneration of the zebrafish heart is driven by the strong proliferation response of its cardiomyocytes to injury. Here we show that, after cardiac injury in zebrafish, telomerase becomes hyperactivated, and telomeres elongate transiently, preceding a peak of cardiomyocyte proliferation and full organ recovery. Using a telomerase-mutant zebrafish model, we found that telomerase loss drastically decreases cardiomyocyte proliferation and fibrotic tissue regression after cryoinjury and that cardiac function does not recover. The impaired cardiomyocyte proliferation response is accompanied by the absence of cardiomyocytes with long telomeres and an increased proportion of cardiomyocytes showing DNA damage and senescence characteristics. These findings demonstrate the importance of telomerase function in heart regeneration and highlight the potential of telomerase therapy as a means of stimulating cell proliferation upon myocardial infarction.

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Stability analysis of a model gene network links aging, stress resistance, and negligible senescence

Valeria Kogan, **Ivan Molodtsov**, **Leonid I. Menshikov**, **Robert J. Shmookler Reis** & **Peter Fedichev** ✉

Several animal species are considered to exhibit what is called negligible senescence, i.e. they do not show signs of functional decline or any increase of mortality with age. Recent studies in naked mole rat and long-lived sea urchins showed that these species do not alter their gene-expression profiles with age as much as other organisms do. This is consistent with exceptional endurance of naked mole rat tissues to various genotoxic stresses. We conjectured, therefore, that the lifelong transcriptional stability of an organism may be a key determinant of longevity. We analyzed the stability of a simple genetic-network model and found that under most common circumstances, such a gene network is inherently unstable. Over a time it undergoes an exponential accumulation of gene-regulation deviations leading to death. However, should the repair systems be sufficiently effective, the gene network can stabilize so that gene damage remains constrained along with mortality of the organism. We investigate the relationship between stress-resistance and aging and suggest that the unstable regime may provide a mathematical basis for the Gompertz “law” of aging in many species. At the same time, this model accounts for the apparently age-independent mortality observed in some exceptionally long-lived animals.

Review

Basic mechanisms of longevity: A case study of *Drosophila* pro-longevity genes

Ekaterina N. Proshkina[a, b, c], Mikhail V. Shaposhnikov[b, c], Asiya F. Sadritdinova[a], Anna V. Kudryavtseva[a], Alexey A. Moskalev[a, b, c, d]

Abstract

Drosophila is one of the most convenient model organisms in the genetics of aging and longevity. Unlike the nematodes, which allow for the detection of new pro-aging genes by knockout and RNAi-mediated knock-down, *Drosophila* also provides an opportunity to find new pro-longevity genes by driver-induced overexpression. Similar studies on other models are extremely rare. In this review we focused on genes whose overexpression prolongs the life of fruit flies. The majority of longevity-associated genes regulates metabolism and stress resistance, and belong to the IGF-1R, PI3K, PKB, AMPK and TOR metabolic regulation cluster and the FOXO, HDAC, p53 stress response cluster.

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Association of the *FOXO3A* Locus with Extreme Longevity in a Southern Italian Centenarian Study

A number of potential candidate genes in a variety of biological pathways have been associated with longevity in model organisms. Many of these genes have human homologs and thus have the potential to provide insights into human longevity. Recently, several studies suggested that *FOXO3A* functions as a key bridge for various signaling pathways that influence aging and longevity. Interestingly, Willcox and colleagues identified several variants that displayed significant genotype–gender interaction in male human longevity. In particular, a nested case–control study was performed in an ethnic Japanese population in Hawaii, and five candidate longevity genes were chosen based on links to the insulin–insulin-like growth factor-1 (IGF-1) signaling pathway. In the Willcox study, the investigated genetic variations (rs2802292, rs2764264, and rs13217795) within the *FOXO3A* gene were significantly associated with longevity in male centenarians. We validated the association of *FOXO3A* polymorphisms with extreme longevity in males from the Southern Italian Centenarian Study. Particularly, rs2802288, a proxy of rs2802292, showed the best allelic association—minor allele frequency (MAF) = 0.49; p = 0.003; odds ratio (OR) = 1.51; 95% confidence interval (CI), 1.15–1.98). Furthermore, we undertook a meta-analysis to explore the significance of rs2802292 association with longevity by combining the association results of the current study and the findings coming from the Willcox et al. investigation. Our data point to a key role of *FOXO3A* in human longevity and confirm the feasibility of the identification of such genes with centenarian–controls studies. Moreover, we hypothesize the susceptibility to the longevity phenotype may well be the result of complex interactions involving genes and environmental factors but also gender.

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Association of growth differentiation factor 11/8, putative anti-ageing factor, with cardiovascular outcomes and overall mortality in humans: analysis of the Heart and Soul and HUNT3 cohorts

Aims Growth differentiation factor 11 and/or its homologue growth differentiation factor 8 (GDF11/8) reverses age-related cardiac hypertrophy and vascular ageing in mice. We investigated whether GDF11/8 associates with cardiovascular outcomes, left ventricular hypertrophy (LVH), or age in humans.

Methods and results We measured plasma GDF11/8 levels in 928 participants with stable ischaemic heart disease in the Heart and Soul study. We adjudicated heart failure hospitalization, stroke, myocardial infarction, death, and their composite endpoint. Left ventricular hypertrophy was evaluated by echocardiography. We used multivariable Cox proportional hazards models to compare rates of cardiovascular events and death across GDF11/8 quartiles and logistic regression models to evaluate the association between GDF11/8 and LVH. Four hundred and fifty participants (48.5%) experienced a cardiovascular event or death during 8.9 years of follow-up. The adjusted risk of the composite endpoint was lower in the highest compared with the lowest GDF11/8 quartile [hazard ratio (HR), 0.45; 95% confidence interval (CI), 0.33–0.60; $P < 0.001$]. We replicated this relationship of GDF11/8 to adverse events in 971 participants in the HUNT3 cohort (adjusted HR, 0.34; 95% CI, 0.23–0.51; $P < 0.001$). Left ventricular hypertrophy was present in 368 participants (39.7%) at baseline. Participants in the highest quartile of GDF11/8 were less likely to have LVH than those in the lowest quartile (adjusted OR, 0.55; 95% CI, 0.35–0.86; $P = 0.009$). GDF11/8 levels were lower in older individuals ($P < 0.001$).

Conclusion In patients with stable ischaemic heart disease, higher GDF11/8 levels are associated with lower risk of cardiovascular events and death. Our findings suggest that GDF11/8 has similar cardioprotective properties in humans to those demonstrated in mice.

Acute Myocardial Infarction Is a Risk Factor for New Onset Diabetes in Patients with Coronary Artery Disease

Chul Soo Park, Woo Baek Chung, Yun Seok Choi, Pum Joon Kim, Jong Min Lee, Ki-Hyun Baek, Hee Yeol Kim, Ki Dong Yoo, Ki-Ho Song, Wook Sung Chung, Ki Bae Seung, Man Young Lee, Hyuk-Sang Kwon

Objective

To test the hypothesis that acute myocardial infarction (AMI) might accelerate development of new onset diabetes in patients with coronary artery disease independent of known risk factors.

Methods

We conducted a retrospective cohort study within COACT (CathOlic medical center percutAneous Coronary inTervention) registry. From a total of 9,127 subjects, 2,036 subjects were diabetes naïve and followed up for at least one year with both index and follow-up laboratory data about diabetes. Cox proportional hazard model was used to derive hazard ratios (HRs) and 95% confidence interval (CI) for new onset diabetes associated with AMI in univariate and multivariate analysis after adjusting several covariates.

Results

The overall hazard for diabetes was higher in AMI compared to non-AMI patients (p by log rank <0.01) with HR of 1.78 and 95% CI of 1.37–2.32 in univariate analysis. This association remained significant after adjusting covariates (HR, 1.54; 95% CI, 1.14–2.07; p<0.01). AMI was an independent predictor for higher quartile of WBC count in multivariate ordinal logistic regression analysis (OR, 6.75; 95% CI, 5.53–8.22, p<0.01). In subgroup analysis, the diabetogenic effect of AMI was more prominent in the subgroup without MetS compared to MetS patients (p for interaction<0.05). Compared to the reference group of non-AMI+nonMetS, the group of AMI+non-MetS (HR, 2.44; 95% CI, 1.58–3.76), non-AMI+MetS (HR, 3.42; 95% CI, 2.34–4.98) and AMI+MetS (HR, 4.12; 95% CI, 2.67–6.36) showed higher HR after adjusting covariates. However, the hazard was not different between the non-AMI+MetS and AMI+non-MetS groups.

Conclusions

AMI patients have a greater risk of new-onset diabetes when compared to non AMI patients, especially those with mild metabolic abnormalities.

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Intake of saturated and trans unsaturated fatty acids and risk of all cause mortality, cardiovascular disease, and type 2 diabetes: systematic review and meta-analysis of observational studies

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Cite this as: *BMJ* 2015;351:h3978

Results For saturated fat, three to 12 prospective cohort studies for each association were pooled (five to 17 comparisons with 90 501-339 090 participants). Saturated fat intake was not associated with all cause mortality (relative risk 0.99, 95% confidence interval 0.91 to 1.09), CVD mortality (0.97, 0.84 to 1.12), total CHD (1.06, 0.95 to 1.17), ischemic stroke (1.02, 0.90 to 1.15), or type 2 diabetes (0.95, 0.88 to 1.03). There was no convincing lack of association between saturated fat and CHD mortality (1.15, 0.97 to 1.36; P=0.10). For trans fats, one to six prospective cohort studies for each association were pooled (two to seven comparisons with 12 942-230 135 participants). Total trans fat intake was associated with all cause mortality (1.34, 1.16 to 1.56), CHD mortality (1.28, 1.09 to 1.50), and total CHD (1.21, 1.10 to 1.33) but not ischemic stroke (1.07, 0.88 to 1.28) or type 2 diabetes (1.10, 0.95 to 1.27). Industrial, but not ruminant, trans fats were associated with CHD mortality (1.18 (1.04 to 1.33) *v* 1.01 (0.71 to 1.43)) and CHD (1.42 (1.05 to 1.92) *v* 0.93 (0.73 to 1.18)). Ruminant *trans*-palmitoleic acid was inversely associated with type 2 diabetes (0.58, 0.46 to 0.74). The certainty of associations between saturated fat and all outcomes was "very low." The certainty of associations of trans fat with CHD outcomes was "moderate" and "very low" to "low" for other associations.

Conclusions Saturated fats are not associated with all cause mortality, CVD, CHD, ischemic stroke, or type 2 diabetes, but the evidence is heterogeneous with methodological limitations. Trans fats are associated with all cause mortality, total CHD, and CHD mortality, probably because of higher levels of intake of industrial trans fats than ruminant trans fats. Dietary guidelines must carefully consider the health effects of recommendations for alternative macronutrients to replace trans fats and saturated fats.

Increased Stiffness in Aged Skeletal Muscle Impairs Muscle Progenitor Cell Proliferative Activity

Grégory Lacraz, André-Jean Rouleau, Vanessa Couture, Thomas Söllrald, Geneviève Drouin, Noémie Veillette, Michel Grandbois, Guillaume Grenier

Background

Skeletal muscle aging is associated with a decreased regenerative potential due to the loss of function of endogenous stem cells or myogenic progenitor cells (MPCs). Aged skeletal muscle is characterized by the deposition of extracellular matrix (ECM), which in turn influences the biomechanical properties of myofibers by increasing their stiffness. Since the stiffness of the MPC microenvironment directly impacts MPC function, we hypothesized that the increase in muscle stiffness that occurs with aging impairs the behavior of MPCs, ultimately leading to a decrease in regenerative potential.

Results

We showed that freshly isolated individual myofibers from aged mouse muscles contain fewer MPCs overall than myofibers from adult muscles, with fewer quiescent MPCs and more proliferative and differentiating MPCs. We observed alterations in cultured MPC behavior in aged animals, where the proliferation and differentiation of MPCs were lower and higher, respectively. These alterations were not linked to the intrinsic properties of aged myofibers, as shown by the similar values for the cumulative population-doubling values and fusion indexes. However, atomic force microscopy (AFM) indentation experiments revealed a nearly 4-fold increase in the stiffness of the MPC microenvironment. We further showed that the increase in stiffness is associated with alterations to muscle ECM, including the accumulation of collagen, which was correlated with higher hydroxyproline and advanced glycation end-product content. Lastly, we recapitulated the impaired MPC behavior observed in aging using a hydrogel substrate that mimics the stiffness of myofibers.

Conclusions

These findings provide novel evidence that the low regenerative potential of aged skeletal muscle is independent of intrinsic MPC properties but is related to the increase in the stiffness of the MPC microenvironment.

A Subset of Cerebrospinal Fluid Proteins from a Multi-Analyte Panel Associated with Brain Atrophy, Disease Classification and Prediction in Alzheimer's Disease

In this exploratory neuroimaging-proteomic study, we aimed to identify CSF proteins associated with AD and test their prognostic ability for disease classification and MCI to AD conversion prediction. Our study sample consisted of 295 subjects with CSF multi-analyte panel data and MRI at baseline downloaded from ADNI. Firstly, we tested the statistical effects of CSF proteins (n = 83) to measures of brain atrophy, CSF biomarkers, ApoE genotype and cognitive decline. We found that several proteins (primarily CgA and FABP) were related to either brain atrophy or CSF biomarkers. In relation to ApoE genotype, a unique biochemical profile characterised by low CSF levels of Apo E was evident in ε4 carriers compared to ε3 carriers. In an exploratory analysis, 3/83 proteins (SGOT, MCP-1, IL6r) were also found to be mildly associated with cognitive decline in MCI subjects over a 4-year period. Future studies are warranted to establish the validity of these proteins as prognostic factors for cognitive decline. For disease classification, a subset of proteins (n = 24) combined with MRI measurements and CSF biomarkers achieved an accuracy of 95.1% (Sensitivity 87.7%; Specificity 94.3%; AUC 0.95) and accurately detected 94.1% of MCI subjects progressing to AD at 12 months. The subset of proteins included FABP, CgA, MMP-2, and PPP as strong predictors in the model. Our findings suggest that the marker of panel of proteins identified here may be important candidates for improving the earlier detection of AD. Further targeted proteomic and longitudinal studies would be required to validate these findings with more generalisability.

JAMA Neurol. 2015 Aug 24. doi: 10.1001/jamaneurol.2015.1721. [Epub ahead of print]

Characterizing Apolipoprotein E ε4 Carriers and Noncarriers With the Clinical Diagnosis of Mild to Moderate Alzheimer Dementia and Minimal β-Amyloid Peptide Plaques.

Monsell SE[1], Kukull WA[2], Roher AE[3], Maarouf CL[4], Serrano G[3], Beach TG[3], Caselli RJ[5], Montine TJ[6], Reiman EM[7].

Author information

Abstract

IMPORTANCE: β-Amyloid peptide (Aβ) plaques are a cardinal neuropathologic feature of Alzheimer disease (AD), yet more than one-third of apolipoprotein E ε4 (APOE4) noncarriers with the clinical diagnosis of mild to moderate Alzheimer dementia may not meet positron emission tomographic criteria for significant cerebral amyloidosis.

OBJECTIVES: To clarify the percentage of APOE4 carriers and noncarriers with the primary clinical diagnosis of mild to moderate Alzheimer dementia near the end of life and minimal Aβ plaques noted at autopsy and the extent to which these cases are associated with appreciable neurofibrillary degeneration or a primary neuropathologic diagnosis other than AD.

DESIGN, SETTING, AND PARTICIPANTS: Data on participants included in this study were obtained from the National Alzheimer Coordinating Center's Uniform Data Set, which comprises longitudinal clinical assessments performed at the AD centers funded by the National Institute on Aging. Neuropathology data are available for the subset of participants who died. A total of 100 APOE4 noncarriers and 100 APOE4 carriers had the primary clinical diagnosis of mild to moderate Alzheimer dementia at their last visit, known APOE4 genotype, died within the ensuing 24 months, and underwent neuropathologic evaluation on autopsy. The study was conducted from September 1, 2005, to September 1, 2012; analysis was performed from October 9, 2012, to March 20, 2015.

MAIN OUTCOMES AND MEASURES: Standardized histopathologic assessments of AD neuropathologic changes were the primary measures of interest in this study, specifically Consortium to Establish a Registry for Alzheimer's Disease neuritic plaque density score, diffuse plaque density score, and Braak stage for neurofibrillary degeneration. The distributions of scores for these measures were the primary outcomes.

RESULTS: Of the 37 APOE4 noncarriers with minimal neuritic plaques, 16 individuals (43.2%) had Braak stages III to VI ratings, and 15 of the others (75.0%) met neuropathologic criteria for other dementia-related diseases. Of the 13 APOE4 carriers with minimal neuritic plaques, 6 individuals (46.2%) had Braak stages III to VI ratings and met neuropathologic criteria for other dementia-related diseases. Similarly, of the 7 APOE4 carriers with minimal neuritic plaques and Braak stages 0 to II, 4 participants (57.1%) were thought to have pathologic changes and alterations resulting from non-AD neuropathologic features.

CONCLUSIONS AND RELEVANCE: In this study, more than one-third of APOE4 noncarriers with the primary clinical diagnosis of mild to moderate Alzheimer dementia had minimal Aβ plaque accumulation in the cerebral cortex and, thus, may show limited or no benefit from otherwise effective anti-Aβ treatment. Almost half of the participants with a primary clinical diagnosis of mild to moderate Alzheimer dementia and minimal Aβ plaque accumulation had an extensive topographic distribution of neurofibrillary degeneration. Additional studies are needed to better understand and provide treatment for patients with this unexpectedly common cliniconeuropathologic condition.

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Blood-Borne Revitalization of the Aged Brain FREE

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In the modern medical era, more diverse and effective treatment options have translated to increased life expectancy. With this increased life span comes increased age-associated disease and the dire need to understand underlying causes so that therapies can be designed to mitigate the burden to health and the economy. Aging exacts a seemingly inevitable multisystem deterioration of function that acts as a risk factor for a variety of age-related disorders, including those that devastate organs of limited regenerative potential, such as the brain. Rather than studying the brain and mechanisms that govern its aging in isolation from other organ systems, an emerging approach is to understand the relatively unappreciated communication that exists between the brain and systemic environment. Revisiting classical methods of experimental physiology in animal models has uncovered surprising regenerative activity in young blood with translational implications for the aging liver, muscle, brain, and other organs. Soluble factors present in young or aged blood are sufficient to improve or impair cognitive function, respectively, suggesting an aging continuum of brain-relevant systemic factors. The age-associated plasma chemokine CCL11 has been shown to impair young brain function while GDF11 has been reported to increase the generation of neurons in aged mice. However, the identities of specific factors mediating memory-enhancing effects of young blood and their mechanisms of action are enigmatic. Here we review brain rejuvenation studies in the broader context of systemic rejuvenation research. We discuss putative mechanisms for blood-borne brain rejuvenation and suggest promising avenues for future research and development of therapies.

Tau Binds to Multiple Tubulin Dimers with Helical Structure

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Understanding the mechanism by which tau binds to and promotes microtubule (MT) assembly as part of its native function may also provide insight into its loss of function that occurs in neurodegenerative disease. Both mechanistic and structural studies of tau have been hindered by its intrinsic disorder and highly dynamic nature. Here, we combine fluorescence correlation spectroscopy and acrylodan fluorescence screening to study the stoichiometry and structural features of tau-tubulin assemblies. Our results show that tau binds to multiple tubulin dimers, even when MT assembly is inhibited. Moreover, we observe helical structure in the repeat regions of the MT binding domain of tau in the tau-tubulin complex, reflecting partial folding upon binding. Our findings support a role for tau's intrinsic disorder in providing a flexible scaffold for binding tubulin and MTs and a disorder-to-order transition in mediating this important interaction.

pH-Dependent Population Shift Regulates BACE1 Activity and Inhibition

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BACE1, a major therapeutic target for treatment of Alzheimer's disease, functions within a narrow pH range. Despite tremendous effort and progress in the development of BACE1 inhibitors, details of the underlying pH-dependent regulatory mechanism remain unclear. Here we elucidate the pH-dependent conformational mechanism that regulates BACE1 activity using continuous constant-pH molecular dynamics (MD). The simulations reveal that BACE1 mainly occupies three conformational states and that the relative populations of the states shift according to pH. At intermediate pH, when the catalytic dyad is monoprotonated, a binding-competent state is highly populated, while at low and high pH a Tyr-inhibited state is dominant. Our data provide strong evidence supporting conformational selection as a major mechanism for substrate and peptide-inhibitor binding. These new insights, while consistent with experiment, greatly extend the knowledge of BACE1 and have implications for further optimization of inhibitors and understanding potential side effects of targeting BACE1. Finally, the work highlights the importance of properly modeling protonation states in MD simulations.

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RNA Binds to Tau Fibrils and Sustains Template-Assisted Growth

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Tau fibrils are the main proteinacious components of neurofibrillary lesions in Alzheimer disease. Although RNA molecules are sequestered into these lesions, their relationship to Tau fibrils is only poorly understood. Such understanding, however, is important, as short fibrils can transfer between neurons and nonproteinacious factors including RNA could play a defining role in modulating the latter process. Here, we used sedimentation assays combined with electron paramagnetic resonance (EPR), fluorescence, and absorbance spectroscopy to determine the effects of RNA on Tau fibril structure and growth. We observe that, in the presence of RNA, three-repeat (3R) and four-repeat (4R) Tau form fibrils with parallel, in-register arrangement of β-strands and exhibit an asymmetric seeding barrier in which 4R Tau grows onto 3R Tau seeds but not vice versa. These structural features are similar to those previously observed for heparin-induced fibrils, indicating that basic conformational properties are conserved, despite their being molecular differences of the nucleating agents. Furthermore, RNA sustains template-assisted growth and binds to the fibril surface and can be exchanged by heparin. These findings suggest that, in addition to mediating fibrillization, cofactors decorating the surface of Tau fibrils may modulate biological interactions and thereby influence the spreading of Tau pathology in the human brain.

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Deamidation of Human γS-Crystallin Increases Attractive Protein Interactions: Implications for Cataract

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Deamidation of proteins is one of the most prevalent post-translational modifications found upon aging, and in age-onset diseases. Specific asparagine and glutamine residues are often selectively deamidated during this process. In the human lens, deamidation has been shown to occur in many crystallins, but it is not clear how these deamidated proteins lead to lens opacity or cataract. Here we have modeled *in vitro* the effect of deamidation of specific asparagine and glutamine residues in human recombinant γS-crystallin (HGS) on the solution properties of the protein. The residues selected for deamidation *in vitro* are those that are found to be deamidated in aged and cataractous lenses *in vivo*. Two derivatives were prepared, one with Asn76 and Asn143 deamidated (2N-HGS) and the other with two additional Gln residues (92 and 120) deamidated (2N2Q-HGS). Isoelectric focusing measurements showed the expected lowering of the pI from 6.9 in HGS to ~6.5 in 2N-HGS and to ~6.1 in 2N2Q-HGS. However, spectroscopic studies showed no significant change in the secondary and tertiary structures of the deamidated proteins relative to the wild type. The stability of 2N-HGS and 2N2Q-HGS, as measured by guanidinium hydrochloride unfolding, also remained comparable to that of HGS. The main difference was the altered protein–protein interaction among the three proteins. The net repulsive interactions that are characteristic of HGS are diminished in the deamidated derivatives as evidenced by static light scattering measurements of the second virial coefficient, B_2 (B_2 values for HGS, 2N-HGS, and 2N2Q-HGS of 8.90×10^{-4}, 7.10×10^{-4}, and 6.65×10^{-4} mL mol g^{-2}, respectively). Further substantiation is provided by estimates of the excess binding energy of protein–protein interactions in the condensed phase, obtained from measurements of the PEG-induced liquid–liquid phase separation profiles for the three proteins. The data suggest that enhanced attractive protein–protein interactions, arising from the deamidation of HGS, promote protein aggregation, thereby leading to increased light scattering and opacity over time.

Reviews/Editorials/Commentaries

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Alzheimer's in 3D culture: Challenges and perspectives.

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Abstract

Alzheimer's disease (AD) is the most common cause of dementia, and there is currently no cure. The "β-amyloid cascade hypothesis" of AD is the basis of current understanding of AD pathogenesis and drug discovery. However, no AD models have fully validated this hypothesis. We recently developed a human stem cell culture model of AD by cultivating genetically modified human neural stem cells in a three-dimensional (3D) cell culture system. These cells were able to recapitulate key events of AD pathology including β-amyloid plaques and neurofibrillary tangles. In this review, we will discuss the progress and current limitations of AD mouse models and human stem cell models as well as explore the breakthroughs of 3D cell culture systems. We will also share our perspective on the potential of dish models of neurodegenerative diseases for studying pathogenic cascades and therapeutic drug discovery.