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Scientific News 7th of December 2014
Sven Bulterijs

Sad news: dr. L. Stephen Coles has died

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Fight Aging!

2014 Challenge Grant

Thanks to Fight Aging! and a generous group of matching fund backers, up to $50,000 donated to SENS Research Foundation before the end of 2014 will be **tripled** in value. Every dollar received will unlock an extra $2 from the grant.

Special thanks to everyone who helped us achieve our $5,000 #GIVINGTUESDAY goal!

Paper by Heales member Edouard!

Biores Open Access. Oct 1, 2014; 3(5): 226–232.
doi: 10.1089/biores.2014.0043
PMCID: PMC4215333

Aged Mice Repeatedly Injected with Plasma from Young Mice: A Survival Study

Dmytro Shytikov,[1] Olexiy Balva,[1] Edouard Debonneuil,[2] Pavel Glukhovskiy,[3] and Iryna Pishel[1]

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Abstract

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It was reported using various biological models that the administration of blood factors from young animals to old animals could rejuvenate certain functions. To assess the anti-aging effect of young blood we tested the influence of repeated injections of plasma from young mice on the lifespan of aged mice. One group of 36 CBA/Ca female mice aged 10–12 months was treated by repeated injections of plasma from 2- to 4-month-old females (averaging 75–150 μL per injection, once intravenously and once intraperitoneally per week for 16 months). Their lifespan was compared to a control group that received saline injections. The median lifespan of mice from the control group was 27 months versus 26.4 months in plasma-treated group; the repeated injections of young plasma did not significantly impact either median or maximal lifespan.

Key words: : aging, immunology

Paper from Belgian research group

Brain Struct Funct. 2014 Nov 9. [Epub ahead of print]

A neuronal aging pattern unique to humans and common chimpanzees.

Gilissen EP[1], Leroy K, Yilmaz Z, Kövari E, Bouras C, Boom A, Poncelet L, Erwin JM, Sherwood CC, Hof PR, Brion JP.

Author information

Abstract

Lipofuscin pigment accumulation is among the most prominent markers of cellular aging in postmitotic cells. The formation of lipofuscin is related to oxidative enzymatic activity and free radical-induced lipid peroxidation. In various mammals such as rat, dog, macaque as well as in cheirogaleid primates, most of the large neurons, such as cerebellar Purkinje cells and neocortical pyramidal cells, show heavy lipofuscin accumulation in adulthood. In contrast, a well-known yet poorly studied feature of the aging human brain is that although lipofuscin accumulation is most marked in large neurons of the cerebral cortex, the large neurons of the cerebellar cortex-the Purkinje cells-appear to remain free of lipofuscin accumulation. It is however, not known whether this characteristic of human Purkinje cells is shared with other primates or other mammals. This study reports results from histological observation of Purkinje cells in humans, non-human primates, and other mammals. Procedures include histochemistry, immunocytochemistry, and fluorescence microscopy. Abundant lipofuscin deposition was observed in Purkinje cells of all the species we examined except Homo sapiens (including Alzheimer's disease cases) and Pan troglodytes. In contrast, lipofuscin deposition was observed in neurons of the dentate nucleus. Our findings suggest that when compared with other primates, Purkinje cells in chimpanzees and humans might share a common aging pattern that involves mechanisms for neuroprotection. This observation is important when considering animal models of aging.

Organelle-Based Aggregation and Retention of Damaged Proteins in Asymmetrically Dividing Cells

Chuankai Zhou, Brian D. Slaughter, Jay R. Unruh, Fengli Guo, Zulin Yu, Kristen Mickey, Akshay Narkar, Rhonda Trimble Ross, Melainia McClain, Rong Li

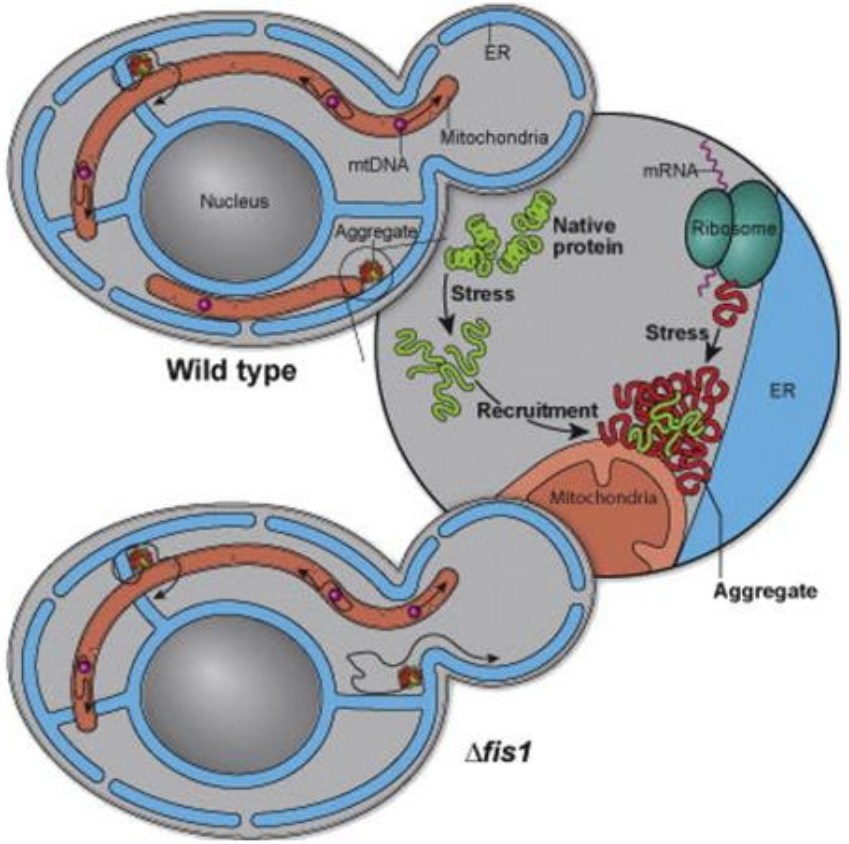
Highlights

- Aggregation of misfolded cytosolic proteins requires active translation
- Aggregation is initiated by newly synthesized polypeptides on the surface of ER
- ER-associated aggregation sites are frequently bound or captured by mitochondria
- Mitochondria control the dynamics and asymmetric segregation of aggregates

Summary

Aggregation of damaged or misfolded proteins is a protective mechanism against proteotoxic stress, abnormalities of which underlie many aging-related diseases. Here, we show that in asymmetrically dividing yeast cells, aggregation of cytosolic misfolded proteins does not occur spontaneously but requires new polypeptide synthesis and is restricted to the surface of ER, which harbors the majority of active translation sites. Protein aggregates formed on ER are frequently also associated with or are later captured by mitochondria, greatly constraining aggregate mobility. During mitosis, aggregates are tethered to well-anchored maternal mitochondria, whereas mitochondria acquired by the bud are largely free of aggregates. Disruption of aggregate-mitochondria association resulted in increased mobility and leakage of mother-accumulated aggregates into the bud. Cells with advanced replicative age exhibit gradual decline of aggregates-mitochondria association, likely contributing to their diminished ability to rejuvenate through asymmetric cell division.

Graphical Abstract



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Aging Cell. 2014 Nov 26. doi: 10.1111/acel.12280. [Epub ahead of print]

Lifespan-extending caloric restriction or mTOR inhibition impair adaptive immunity of old mice by distinct mechanisms.

Goldberg EL[1], Romero-Aleshire MJ, Renkema KR, Ventevogel MS, Chew WM, Uhrlaub JL, Smithey MJ, Limesand KH, Sempowski GD, Brooks HL, Nikolich-Žugich J.

Author information

Abstract

Aging of the world population and a concomitant increase in age-related diseases and disabilities mandates the search for strategies to increase healthspan, the length of time an individual lives healthy and productively. Due to the age-related decline of the immune system, infectious diseases remain among the top 5-10 causes of mortality and morbidity in the elderly, and improving immune function during aging remains an important aspect of healthspan extension. Calorie restriction (CR) and more recently rapamycin (rapa) feeding have both been used to extend lifespan in mice. Preciously few studies have actually investigated the impact of each of these interventions upon in vivo immune defense against relevant microbial challenge in old organisms. We tested how rapa and CR each impacted the immune system in adult and old mice. We report that each intervention differentially altered T-cell development in the thymus, peripheral T-cell maintenance, T-cell function and host survival after West Nile virus infection, inducing distinct but deleterious consequences to the aging immune system. We conclude that neither rapa feeding nor CR, in the current form/administration regimen, may be optimal strategies for extending healthy immune function and, with it, lifespan.

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Young capillary vessels rejuvenate aged pancreatic islets

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Author Affiliations

Abstract

Pancreatic islets secrete hormones that play a key role in regulating blood glucose levels (glycemia). Age-dependent impairment of islet function and concomitant dysregulation of glycemia are major health threats in aged populations. However, the major causes of the age-dependent decline of islet function are still disputed. Here we demonstrate that aging of pancreatic islets in mice and humans is notably associated with inflammation and fibrosis of islet blood vessels but does not affect glucose sensing and the insulin secretory capacity of islet beta cells. Accordingly, when transplanted into the anterior chamber of the eye of young mice with diabetes, islets from old mice are revascularized with healthy blood vessels, show strong islet cell proliferation, and fully restore control of glycemia. Our results indicate that beta cell function does not decline with age and suggest that islet function is threatened by an age-dependent impairment of islet vascular function. Strategies to mitigate age-dependent dysregulation in glycemia should therefore target systemic and/or local inflammation and fibrosis of the aged islet vasculature.

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Clin Interv Aging. 2014 Nov 19;9:1981-6. doi: 10.2147/CIA.S71130. eCollection 2014.

Soluble receptor for advanced glycation end products in critically ill patients and its associations with other clinical markers and 28-day mortality.

Cheng Y[1], Zhong J[1], Xiang Y[1], Zeng F[1], Cai D[2], Zhao L[1].

⊕ Author information

Abstract

PURPOSE: To investigate the possible associations between serum levels of soluble receptor for advanced glycation end products (sRAGE) and specific clinical markers and prognosis in critically ill patients diagnosed with stress hyperglycemia.

PATIENTS AND METHODS: A total of 70 critically ill patients and 25 normal controls were recruited for this study. Serum levels of sRAGE and advanced glycation end products (AGEs) were determined using enzyme-linked immunosorbent assay. Additional data on other clinical markers were obtained from patient records in the intensive care unit. Comparisons of sRAGE and AGEs levels between groups were assessed by t-test. The relationships between sRAGE and other clinical markers were assessed by Pearson's correlation analyses and multiple linear regression analyses. Risk factors for prognosis, such as 28-day mortality were analyzed using logistic regression analysis.

RESULTS: Serum sRAGE and AGEs levels were significantly higher in critically ill patients, compared to normal controls ($P<0.05$). The increase in serum sRAGE levels was significantly correlated with AGEs levels, interleukin-6 levels, and the sequential organ failure assessment score ($P<0.01$). Using multiple linear regression analysis, the association between AGEs and sRAGE remained significant after adjustment of other clinical factors. However, there were no significant correlations between sRAGE levels and patient outcome in these critically ill patients.

CONCLUSION: Serum sRAGE levels were significantly elevated in critically ill patients and positively correlated with higher AGEs levels, but sRAGE levels were not associated with increased mortality, suggesting sRAGE levels are not a predictor of prognosis in critically ill patients.

KEYWORDS: advanced glycation end products; critically ill patients; predictor; relationship; soluble receptor for advanced glycation end products

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Aging Cell. 2014 Oct;13(5):935-45. doi: 10.1111/acel.12254. Epub 2014 Jul 25.

Neuronal glycogen synthesis contributes to physiological aging.

Sinadinos C[1], Valles-Ortega J, Boulan L, Solsona E, Tevy MF, Marquez M, Duran J, Lopez-Iglesias C, Calbó J, Blasco E, Pumarola M, Milán M, Guinovart JJ.

Author information

Abstract

Glycogen is a branched polymer of glucose and the carbohydrate energy store for animal cells. In the brain, it is essentially found in glial cells, although it is also present in minute amounts in neurons. In humans, loss-of-function mutations in laforin and malin, proteins involved in suppressing glycogen synthesis, induce the presence of high numbers of insoluble polyglucosan bodies in neuronal cells. Known as Lafora bodies (LBs), these deposits result in the aggressive neurodegeneration seen in Lafora's disease. Polysaccharide-based aggregates, called corpora amylacea (CA), are also present in the neurons of aged human brains. Despite the similarity of CA to LBs, the mechanisms and functional consequences of CA formation are yet unknown. Here, we show that wild-type laboratory mice also accumulate glycogen-based aggregates in the brain as they age. These structures are immunopositive for an array of metabolic and stress-response proteins, some of which were previously shown to aggregate in correlation with age in the human brain and are also present in LBs. Remarkably, these structures and their associated protein aggregates are not present in the aged mouse brain upon genetic ablation of glycogen synthase. Similar genetic intervention in Drosophila prevents the accumulation of glycogen clusters in the neuronal processes of aged flies. Most interestingly, targeted reduction of Drosophila glycogen synthase in neurons improves neurological function with age and extends lifespan. These results demonstrate that neuronal glycogen accumulation contributes to physiological aging and may therefore constitute a key factor regulating age-related neurological decline in humans.

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Arterioscler Thromb Vasc Biol. 2014 Sep;34(9):1942-52. doi: 10.1161/ATVBAHA.114.303342. Epub 2014 Jul 24.

Induction of lysosomal biogenesis in atherosclerotic macrophages can rescue lipid-induced lysosomal dysfunction and downstream sequelae.

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Author information

Abstract

OBJECTIVE: Recent reports of a proatherogenic phenotype in mice with macrophage-specific autophagy deficiency have renewed interest in the role of the autophagy-lysosomal system in atherosclerosis. Lysosomes have the unique ability to process both exogenous material, including lipids and autophagy-derived cargo such as dysfunctional proteins/organelles. We aimed to understand the effects of an atherogenic lipid environment on macrophage lysosomes and to evaluate novel ways to modulate this system.

APPROACH AND RESULTS: Using a variety of complementary techniques, we show that oxidized low-density lipoproteins and cholesterol crystals, commonly encountered lipid species in atherosclerosis, lead to profound lysosomal dysfunction in cultured macrophages. Disruptions in lysosomal pH, proteolytic capacity, membrane integrity, and morphology are readily seen. Using flow cytometry, we find that macrophages isolated from atherosclerotic plaques also display features of lysosome dysfunction. We then investigated whether enhancing lysosomal function can be beneficial. Transcription factor EB (TFEB) is the only known transcription factor that is a master regulator of lysosomal biogenesis although its role in macrophages has not been studied. Lysosomal stress induced by chloroquine or atherogenic lipids leads to TFEB nuclear translocation and activation of lysosomal and autophagy genes. TFEB overexpression in macrophages further augments this prodegradative response and rescues several deleterious effects seen with atherogenic lipid loading as evidenced by blunted lysosomal dysfunction, reduced secretion of the proinflammatory cytokine interleukin-1β, enhanced cholesterol efflux, and decreased polyubiquitinated protein aggregation.

CONCLUSIONS: Taken together, these data demonstrate that lysosomal function is markedly impaired in atherosclerosis and suggest that induction of a lysosomal biogenesis program in macrophages has antiatherogenic effects.

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Aging Increases the Susceptivity of MSCs to Reactive Oxygen Species and Impairs Their Therapeutic Potency for Myocardial Infarction

Liang Li, Yingfei Guo, Hongxia Zhai, Yaxin Yin, Jinjin Zhang, Haiwei Chen, Lei Wang, Na Li, Runmei Liu, Yunfeng Xia

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Myocardial infarction (MI) is one of the leading causes of death worldwide and Mesenchymal Stem Cells (MSCs) transplantation has been considered a promising therapy. Recently, it was reported that the therapeutic effectiveness of MSCs is dependent on the age of the donor, yet the underlying mechanism has not been thoroughly investigated. This study was designed to investigate whether this impaired therapeutic potency is caused by an increased susceptivity of MSCs from old donors to reactive oxygen species (ROS). The MSCs were isolated from the subcutaneous inguinal region of young (8–10 weeks) and old (18 months) Sprague–Dawley (SD) rats. By exposing these MSCs to H_2O_2, we found that the adhesion of MSCs from old donors was damaged more severely. Specifically, decreased expression of integrin and reduced phosphorylation of focal adhesion kinase Src and FAK were observed. Furthemore, H_2O_2 triggered an increased apoptosis of MSCs from old donors. To study the viability and therapeutic potency of MSCs from young and old donors *in vivo*, these MSCs were transplanted into acute MI model rats. We observed a more rapidly decreased survival rate of the old MSCs in the infarct region, which may be caused by their increased susceptivity to the micro-environmental ROS, as transplantation of the old MSCs with N-acetyl-L-cysteine (NAC), a ROS scavenger, protected them. The low viability of engrafted old MSCs consequently impaired their therapeutic effectiveness, judging by the histology and function of heart. Our study may help to understand the mechanism of MSCs-host interaction during MI, as well as shed light on the design of therapeutic strategy in clinic.

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Whole-Genome Sequencing of the World's Oldest People

Hinco J. Gierman, Kristen Fortney, Jared C. Roach, Natalie S. Coles, Hong Li, Gustavo Glusman, Glenn J. Markov, Justin D. Smith, Leroy Hood, L. Stephen Coles, Stuart K. Kim

Supercentenarians (110 years or older) are the world's oldest people. Seventy four are alive worldwide, with twenty two in the United States. We performed whole-genome sequencing on 17 supercentenarians to explore the genetic basis underlying extreme human longevity. We found no significant evidence of enrichment for a single rare protein-altering variant or for a gene harboring different rare protein altering variants in supercentenarian compared to control genomes. We followed up on the gene most enriched for rare protein-altering variants in our cohort of supercentenarians, TSHZ3, by sequencing it in a second cohort of 99 long-lived individuals but did not find a significant enrichment. The genome of one supercentenarian had a pathogenic mutation in DSC2, known to predispose to arrhythmogenic right ventricular cardiomyopathy, which is recommended to be reported to this individual as an incidental finding according to a recent position statement by the American College of Medical Genetics and Genomics. Even with this pathogenic mutation, the proband lived to over 110 years. The entire list of rare protein-altering variants and DNA sequence of all 17 supercentenarian genomes is available as a resource to assist the discovery of the genetic basis of extreme longevity in future studies.