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Sven Bulterijs

New Science Column on LongeCity

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Welcome to the ICD-10 code for sarcopenia

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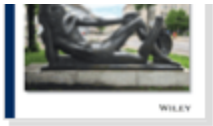

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Abstract

The new ICD-10-CM (M62.84) code for sarcopenia represents a major step forward in recognizing sarcopenia as a disease. This should lead to an increase in availability of diagnostic tools and the enthusiasm for pharmacological companies to develop drugs for sarcopenia.

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A Comparison of the Prevalence of Dementia in the United States in 2000 and 2012

Main Outcomes and Measures Dementia was identified in each year using HRS cognitive measures and validated methods for classifying self-respondents, as well as those represented by a proxy. Logistic regression was used to identify socioeconomic and health variables associated with change in dementia prevalence between 2000 and 2012.

Results The study cohorts had an average age of 75.0 years (95% CI, 74.8-75.2 years) in 2000 and 74.8 years (95% CI, 74.5-75.1 years) in 2012 ($P=.24$); 58.4% (95% CI, 57.3%-59.4%) of the 2000 cohort was female compared with 56.3% (95% CI, 55.5%-57.0%) of the 2012 cohort ($P<.001$). Dementia prevalence among those 65 years or older decreased from 11.6% (95% CI, 10.7%-12.7%) in 2000 to 8.8% (95% CI, 8.2%-9.4%) (8.6% with age- and sex-standardization) in 2012 ($P<.001$). More years of education was associated with a lower risk for dementia, and average years of education increased significantly (from 11.8 years [95% CI, 11.6-11.9 years] to 12.7 years [95% CI, 12.6-12.9 years]; $P<.001$) between 2000 and 2012. The decline in dementia prevalence occurred even though there was a significant age- and sex-adjusted increase between years in the cardiovascular risk profile (eg, prevalence of hypertension, diabetes, and obesity) among older US adults.

Conclusions and Relevance The prevalence of dementia in the United States declined significantly between 2000 and 2012. An increase in educational attainment was associated with some of the decline in dementia prevalence, but the full set of social, behavioral, and medical factors contributing to the decline is still uncertain. Continued monitoring of trends in dementia incidence and prevalence will be important for better gauging the full future societal impact of dementia as the number of older adults increases in the decades ahead.

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The emergence of longevous populations

Abstract

The human lifespan has traversed a long evolutionary and historical path, from short-lived primate ancestors to contemporary Japan, Sweden, and other longevity frontrunners. Analyzing this trajectory is crucial for understanding biological and sociocultural processes that determine the span of life. Here we reveal a fundamental regularity. Two straight lines describe the joint rise of life expectancy and lifespan equality: one for primates and the second one over the full range of human experience from average lifespans as low as 2 y during mortality crises to more than 87 y for Japanese women today. Across the primate order and across human populations, the lives of females tend to be longer and less variable than the lives of males, suggesting deep evolutionary roots to the male disadvantage. Our findings cast fresh light on primate evolution and human history, opening directions for research on inequality, sociality, and aging.

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A single heterochronic blood exchange reveals rapid inhibition of multiple tissues by old blood

Heterochronic parabiosis rejuvenates the performance of old tissue stem cells at some expense to the young, but whether this is through shared circulation or shared organs is unclear. Here we show that heterochronic blood exchange between young and old mice without sharing other organs, affects tissues within a few days, and leads to different outcomes than heterochronic parabiosis. Investigating muscle, liver and brain hippocampus, in the presence or absence of muscle injury, we find that, in many cases, the inhibitory effects of old blood are more pronounced than the benefits of young, and that peripheral tissue injury compounds the negative effects. We also explore mechanistic explanations, including the role of B2M and TGF-beta. We conclude that, compared with heterochronic parabiosis, heterochronic blood exchange in small animals is less invasive and enables better-controlled studies with more immediate translation to therapies for humans.

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Selective removal of deletion-bearing mitochondrial DNA in heteroplasmic Drosophila

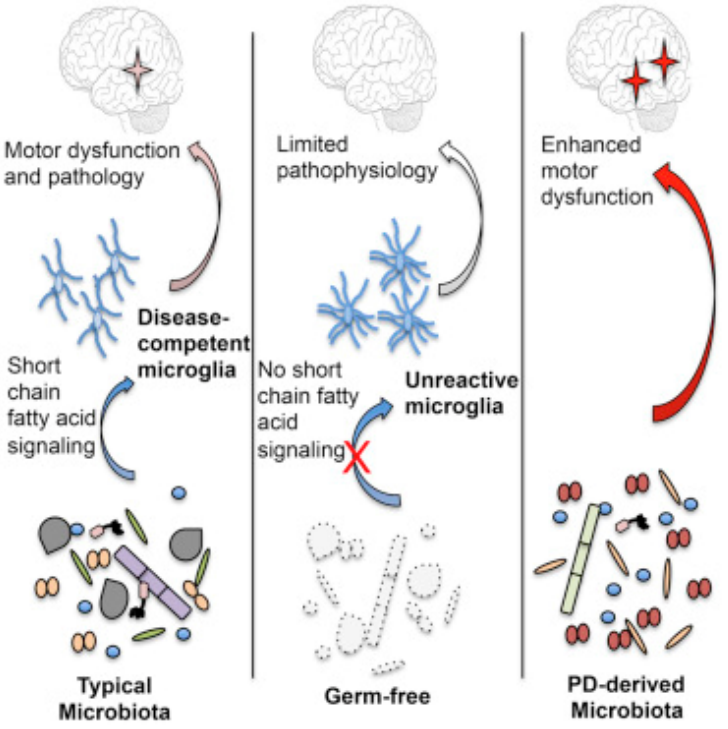
Mitochondrial DNA (mtDNA) often exists in a state of heteroplasmy, in which mutant mtDNA co-exists in cells with wild-type mtDNA. High frequencies of pathogenic mtDNA result in maternally inherited diseases; maternally and somatically acquired mutations also accumulate over time and contribute to diseases of ageing. Reducing heteroplasmy is therefore a therapeutic goal and *in vivo* models in post-mitotic tissues are needed to facilitate these studies. Here we describe a transgene-based model of a heteroplasmic lethal mtDNA deletion ($mtDNA^{\Delta}$) in adult *Drosophila* muscle. Stimulation of autophagy, activation of the *PINK1/parkin* pathway or decreased levels of *mitofusin* result in a selective decrease in $mtDNA^{\Delta}$. Decreased levels of *mitofusin* and increased levels of ATPIF1, an inhibitor of ATP synthase reversal-dependent mitochondrial repolarization, result in a further decrease in $mtDNA^{\Delta}$ levels. These results show that an adult post-mitotic tissue can be cleansed of a deleterious genome, suggesting that therapeutic removal of mutant mtDNA can be achieved.

Gut Microbiota Regulate Motor Deficits and Neuroinflammation in a Model of Parkinson's Disease

Highlights

- Gut microbes promote α-synuclein-mediated motor deficits and brain pathology
- Depletion of gut bacteria reduces microglia activation
- SCFAs modulate microglia and enhance PD pathophysiology
- Human gut microbiota from PD patients induce enhanced motor dysfunction in mice

Graphical Abstract



Summary

The intestinal microbiota influence neurodevelopment, modulate behavior, and contribute to neurological disorders. However, a functional link between gut bacteria and neurodegenerative diseases remains unexplored. Synucleinopathies are characterized by aggregation of the protein α-synuclein (αSyn), often resulting in motor dysfunction as exemplified by Parkinson's disease (PD). Using mice that overexpress αSyn, we report herein that gut microbiota are required for motor deficits, microglia activation, and αSyn pathology. Antibiotic treatment ameliorates, while microbial re-colonization promotes, pathophysiology in adult animals, suggesting that postnatal signaling between the gut and the brain modulates disease. Indeed, oral administration of specific microbial metabolites to germ-free mice promotes neuroinflammation and motor symptoms. Remarkably, colonization of αSyn-overexpressing mice with microbiota from PD-affected patients enhances physical impairments compared to microbiota transplants from healthy human donors. These findings reveal that gut bacteria regulate movement disorders in mice and suggest that alterations in the human microbiome represent a risk factor for PD.

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Phenotypic Screen for Cardiac Regeneration Identifies Molecules with Differential Activity in Human Epicardium-Derived Cells versus Cardiac Fibroblasts

Activation and proliferation of resident cardiac progenitor cells has therapeutic potential to repair the heart after injury. However, research has been impeded by a lack of well-defined and characterized cell sources and difficulties in translation to screening platforms. Here, we describe the development, validation, and use of a 384-well phenotypic assay in primary human epicardium-derived cells (EPDCs) to identify compounds that induce proliferation while maintaining the progenitor phenotype. Using this assay, we screened 7400 structurally diverse compounds where greater than 90% are biologically annotated and known to modulate a broad range of biological targets. From the primary screen, we identified and validated hits and expanded upon the lead molecules of interest. A counterscreen was developed in human cardiac fibroblasts to filter out compounds with a general proliferative effect, after which the activity of selected molecules was confirmed across multiple EPDC donors. To further examine the mechanism of action of compounds with annotated targets, we performed knockdown experiments to understand whether a single known target was responsible for the proliferative effect, confirming results with protein expression and activity assays. Here, we were able to show that the annotated targets of compounds of interest were not responsible for the proliferative effect, which highlights potential differences in cell types and signaling pathways and possible polypharmacology. These studies demonstrate the feasibility of using relevant human primary cells in a phenotypic screen to identify compounds as novel biological tools and starting points for drug discovery projects, and we disclose the first small molecules to proliferate human primary EPDCs.

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Aβ Amyloid Pathology Affects the Hearts of Patients With Alzheimer's Disease

Background Individually, heart failure (HF) and Alzheimer's disease (AD) are severe threats to population health, and their potential coexistence is an alarming prospect. In addition to sharing analogous epidemiological and genetic profiles, biochemical characteristics, and common triggers, the authors recently recognized common molecular and pathological features between the 2 conditions. Whereas cognitive impairment has been linked to HF through perfusion defects, angiopathy, and inflammation, whether patients with AD present with myocardial dysfunction, and if the 2 conditions bear a common pathogenesis as neglected siblings are unknown.

Objectives Here, the authors investigated whether amyloid beta (Aβ) protein aggregates are present in the hearts of patients with a primary diagnosis of AD, affecting myocardial function.

Methods The authors examined myocardial function in a retrospective cross-sectional study from a cohort of AD patients and age-matched controls. Imaging and proteomics approaches were used to identify and quantify Aβ deposits in AD heart and brain specimens compared with controls. Cell shortening and calcium transients were measured on isolated adult cardiomyocytes.

Results Echocardiographic measurements of myocardial function suggest that patients with AD present with an anticipated diastolic dysfunction. As in the brain, Aβ40 and Aβ42 are present in the heart, and their expression is increased in AD.

Conclusions Here, the authors provide the first report of the presence of compromised myocardial function and intramyocardial deposits of Aβ in AD patients. The findings depict a novel biological framework in which AD may be viewed either as a systemic disease or as a metastatic disorder leading to heart, and possibly multiorgan failure. AD and HF are both debilitating and life-threatening conditions, affecting enormous patient populations. Our findings underline a previously dismissed problem of a magnitude that will require new diagnostic approaches and treatments for brain and heart disease, and their combination.

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Comparative analyses of longevity and senescence reveal variable survival benefits of living in zoos across mammals

While it is commonly believed that animals live longer in zoos than in the wild, this assumption has rarely been tested. We compared four survival metrics (longevity, baseline mortality, onset of senescence and rate of senescence) between both sexes of free-ranging and zoo populations of more than 50 mammal species. We found that mammals from zoo populations generally lived longer than their wild counterparts (84% of species). The effect was most notable in species with a faster pace of life (i.e. a short life span, high reproductive rate and high mortality in the wild) because zoos evidently offer protection against a number of relevant conditions like predation, intraspecific competition and diseases. Species with a slower pace of life (i.e. a long life span, low reproduction rate and low mortality in the wild) benefit less from captivity in terms of longevity; in such species, there is probably less potential for a reduction in mortality. These findings provide a first general explanation about the different magnitude of zoo environment benefits among mammalian species, and thereby highlight the effort that is needed to improve captive conditions for slow-living species that are particularly susceptible to extinction in the wild.

REVIEWS/COMMENTS/EDITORIALS

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INSIGHT: NEURODEGENERATIVE DISEASES

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Neurodegeneration: From cellular concepts to clinical applications

Alla Katsnelson[1], Bart De Strooper[2,3,*] and Huda Y. Zoghbi[4,*]

Abstract

Developing therapies for neurodegenerative diseases will require new scientific approaches that take into account the detrimental effects of altered protein and RNA homeostasis on brain cells, the vulnerabilities of various organelles in certain diseases and aging neurons, and the complex multicellular interactions of the nervous system.

Mouse models of ageing and their relevance to disease

Abstract

Ageing is a process that gradually increases the organism's vulnerability to death. It affects different biological pathways, and the underlying cellular mechanisms are complex. In view of the growing disease burden of ageing populations, increasing efforts are being invested in understanding the pathways and mechanisms of ageing. We review some mouse models commonly used in studies on ageing, highlight the advantages and disadvantages of the different strategies, and discuss their relevance to disease susceptibility. In addition to addressing the genetics and phenotypic analysis of mice, we discuss examples of models of delayed or accelerated ageing and their modulation by caloric restriction.

OTHER RESEARCH

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Posttranslational mutagenesis: A chemical strategy for exploring protein side-chain diversity

Posttranslational modification of proteins expands their structural and functional capabilities beyond those directly specified by the genetic code. However, the vast diversity of chemically-plausible (including unnatural but functionally relevant) side-chains is not readily accessible. We describe C (sp^3)–C (sp^3) bond-forming reactions on proteins under biocompatible conditions, which exploit unusual carbon free radical chemistry, and use them to form Cβ–Cγ bonds with altered side chains. We demonstrate how these transformations enable a wide-diversity of natural, unnatural, posttranslationally-modified (methylated, glycosylated, phosphorylated, hydroxylated) and labeled (fluorinated, isotopically-labeled) side-chains to be added to a common, readily-accessible dehydroalanine precursor in a range of representative protein types and scaffolds. This approach, outside of the rigid constraints of the ribosome and enzymatic processing, may be modified more generally for accessing diverse proteins.