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Scientific News
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Sven Bulterijs

The Business of Anti-Aging Science

João Pedro de Magalhães, Michael Stevens, Daniel Thornton

Age-related conditions are the leading causes of death and health-care costs. Reducing the rate of aging would have enormous medical and financial benefits. Myriad genes and pathways are known to regulate aging in model organisms, fostering a new crop of anti-aging companies. Approaches range from drug discovery efforts to big-data methods and direct-to-consumer (DTC) strategies. Challenges and pitfalls of commercialization include reliance on findings from short-lived model organisms, poor biological understanding of aging, and hurdles in performing clinical trials for aging. A large number of potential aging-associated interventions and targets exist, but given the long validation times only a small fraction can be explored for clinical applications. If even one company succeeds, however, the impact will be huge.

Trends

It is increasingly being recognized that directly targeting the aging process, as opposed to individual aging-related diseases or symptoms, is a viable strategy. This is leading to R&D with the ultimate aim of commercializing therapies directed at slowing aging itself.

Some therapeutic approaches – direct-to-consumer nutraceuticals and trial-tested scientific diets – do not require FDA approval, which can significantly reduce their time to market.

To slow the aging process, nonstandard therapies such as blood-based therapies are also being tried.

Big-data approaches are being harnessed in an attempt to build models of healthy aging.

Approaches are increasingly coming directly from aging results in model organisms.

PDF

What is the ethics of ageing?

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Abstract

Applied ethics is home to numerous productive subfields such as procreative ethics, intergenerational ethics and environmental ethics. By contrast, there is far less ethical work on ageing, and there is no boundary work that attempts to set the scope for 'ageing ethics' or the 'ethics of ageing'. Yet ageing is a fundamental aspect of life; arguably even more fundamental and ubiquitous than procreation. To remedy this situation, I examine conceptions of what the ethics of ageing might mean and argue that these conceptions fail to capture the requirements of the desired subfield. The key reasons for this are, first, that they view ageing as something that happens only when one is old, thereby ignoring the fact that ageing is a process to which we are all subject, and second that the ageing person is treated as an object in ethical discourse rather than as its subject. In response to these shortcomings I put forward a better conception, one which places the ageing person at the centre of ethical analysis, has relevance not just for the elderly and provides a rich yet workable scope. While clarifying and justifying the conceptual boundaries of the subfield, the proposed scope pleasingly broadens the ethics of ageing beyond common negative associations with ageing.

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Targeting cellular senescence prevents age-related bone loss in mice.

Farr JN[1], Xu M[1], Weivoda MM[1], Monroe DG[1], Fraser DG[1], Onken JL[1], Negley BA[1], Sfeir JG[1], Ogrodnik MB[1], Hachfeld CM[1], LeBrasseur NK[1], Drake MT[1], Pignolo RJ[1], Pirtskhalava T[1], Tchkonia T[1], Oursler MJ[1], Kirkland JL[1], Khosla S[1].

Author information

Abstract

Aging is associated with increased cellular senescence, which is hypothesized to drive the eventual development of multiple comorbidities. Here we investigate a role for senescent cells in age-related bone loss through multiple approaches. In particular, we used either genetic (i.e., the INK-ATTAC 'suicide' transgene encoding an inducible caspase 8 expressed specifically in senescent cells) or pharmacological (i.e., 'senolytic' compounds) means to eliminate senescent cells. We also inhibited the production of the proinflammatory secretome of senescent cells using a JAK inhibitor (JAKi). In aged (20- to 22-month-old) mice with established bone loss, activation of the INK-ATTAC caspase 8 in senescent cells or treatment with senolytics or the JAKi for 2-4 months resulted in higher bone mass and strength and better bone microarchitecture than in vehicle-treated mice. The beneficial effects of targeting senescent cells were due to lower bone resorption with either maintained (trabecular) or higher (cortical) bone formation as compared to vehicle-treated mice. In vitro studies demonstrated that senescent-cell conditioned medium impaired osteoblast mineralization and enhanced osteoclast-progenitor survival, leading to increased osteoclastogenesis. Collectively, these data establish a causal role for senescent cells in bone loss with aging, and demonstrate that targeting these cells has both anti-resorptive and anabolic effects on bone. Given that eliminating senescent cells and/or inhibiting their proinflammatory secretome also improves cardiovascular function, enhances insulin sensitivity, and reduces frailty, targeting this fundamental mechanism to prevent age-related bone loss suggests a novel treatment strategy not only for osteoporosis, but also for multiple age-related comorbidities.

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Hypothalamic stem cells control ageing speed partly through exosomal miRNAs

It has been proposed that the hypothalamus helps to control ageing, but the mechanisms responsible remain unclear. Here we develop several mouse models in which hypothalamic stem/progenitor cells that co-express Sox2 and Bmi1 are ablated, as we observed that ageing in mice started with a substantial loss of these hypothalamic cells. Each mouse model consistently displayed acceleration of ageing-like physiological changes or a shortened lifespan. Conversely, ageing retardation and lifespan extension were achieved in mid-aged mice that were locally implanted with healthy hypothalamic stem/progenitor cells that had been genetically engineered to survive in the ageing-related hypothalamic inflammatory microenvironment. Mechanistically, hypothalamic stem/progenitor cells contributed greatly to exosomal microRNAs (miRNAs) in the cerebrospinal fluid, and these exosomal miRNAs declined during ageing, whereas central treatment with healthy hypothalamic stem/progenitor cell-secreted exosomes led to the slowing of ageing. In conclusion, ageing speed is substantially controlled by hypothalamic stem cells, partially through the release of exosomal miRNAs.

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Combined impact of healthy lifestyle factors on lifespan: two prospective cohorts

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Abstract. Larsson SC, Kaluza J, Wolk A (Karolinska Institutet, Stockholm, Sweden; Warsaw University of Life Sciences-SGGW, Warsaw, Poland). Combined impact of healthy lifestyle factors on lifespan: two prospective cohorts. *J Intern Med* 2017; **282**: 209–219.

Background. The impact of multiple healthy lifestyle factors on survival time is unclear.

Objective. The aim of this study was to examine differences in survival time associated with a healthy lifestyle versus a less healthy lifestyle.

Methods. This study consisted of 33 454 men (Cohort of Swedish Men) and 30 639 women (Swedish Mammography Cohort) aged 45–83 years and free of cancer and cardiovascular disease at baseline. The healthy lifestyle factors included the following: (i) nonsmoking; (ii) physical activity at least 150 min per week; (iii) alcohol consumption of 0–14 drinks per week; (iv) and healthy diet defined as a modified Dietary Approaches to Stop Hypertension Diet score above the median. Cox proportional hazards regression models and Laplace regression were used to estimate, respectively, hazard ratios of all-cause mortality and differences in survival time.

Results. During follow-up from 1998 through 2014, 8630 deaths amongst men and 6730 deaths amongst women were ascertained through linkage to the Swedish Cause of Death Register. Each of the four healthy lifestyle factors was inversely associated with all-cause mortality and increased survival time. Compared with individuals with no or one healthy lifestyle factor, the multivariable hazard ratios of all-cause mortality for individuals with all four health behaviours were 0.47 (95% 95% confidence interval [CI]: 0.44–0.51) in men and 0.39 (95% CI: 0.35–0.44) in women. This corresponded to a difference in survival time of 4.1 (95% CI: 3.6–4.6) years in men and 4.9 (95% CI: 4.3–5.6) years in women.

Conclusion. Adopting healthy lifestyle behaviours may markedly increase lifespan.

Keywords: lifestyle, lifespan, mortality, prospective studies, survival time.

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Wide-scale comparative analysis of longevity genes and interventions

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Hundreds of genes, when manipulated, affect the lifespan of model organisms (yeast, worm, fruit fly, and mouse) and thus can be defined as longevity-associated genes (LAGs). A major challenge is to determine whether these LAGs are model-specific or may play a universal role as longevity regulators across diverse taxa. A wide-scale comparative analysis of the 1805 known LAGs across 205 species revealed that (i) LAG orthologs are substantially overrepresented, from bacteria to mammals, compared to the entire genomes or interactomes, and this was especially noted for essential LAGs; (ii) the effects on lifespan, when manipulating orthologous LAGs in different model organisms, were mostly concordant, despite a high evolutionary distance between them; (iii) LAGs that have orthologs across a high number of phyla were enriched in translational processes, energy metabolism, and DNA repair genes; (iv) LAGs that have no orthologs out of the taxa in which they were discovered were enriched in autophagy (Ascomycota/Fungi), G proteins (Nematodes), and neuroactive ligand–receptor interactions (Chordata). The results also suggest that antagonistic pleiotropy might be a conserved principle of aging and highlight the importance of overexpression studies in the search for longevity regulators.

Cardiac and systemic rejuvenation after cardiosphere-derived cell therapy in senescent rats

Methods and Results

We compared intra-cardiac injections of neonatal rat CDCs to vehicle (phosphate-buffered saline, PBS) in 21.8 ± 1.6 month-old rats (mean ± standard deviation; $n = 23$ total). Ten rats 4.1 ± 1.5 months of age comprised a young reference group. Blood, echocardiographic, haemodynamic and treadmill stress tests were performed at baseline in all animals, and 1 month after treatment in old animals. Histology and the transcriptome were assessed after terminal phenotyping. For *in vitro* studies, human heart progenitors from older donors, or cardiomyocytes from aged rats were exposed to human CDCs or exosomes secreted by CDCs (CDC-XO) from paediatric donors. Transcriptomic analysis revealed that CDCs, but not PBS, recapitulated a youthful pattern of gene expression in the hearts of old animals (85.5% of genes differentially expressed, $P < 0.05$). Telomeres in heart cells were longer in CDC-transplanted animals ($P < 0.0001$ vs. PBS). Cardiosphere-derived cells attenuated hypertrophy by echo ($P < 0.01$); histology confirmed decreases in cardiomyocyte area ($P < 0.0001$) and myocardial fibrosis ($P < 0.05$) vs. PBS. Cardiosphere-derived cell injection improved diastolic dysfunction [lower E/A ($P < 0.01$), E/E' ($P = 0.05$), end-diastolic pressure-volume relationship ($P < 0.05$) compared with baseline), and lowered serum brain natriuretic peptide (both $P < 0.05$ vs. PBS). In CDC-transplanted old rats, exercise capacity increased ~20% ($P < 0.05$ vs. baseline), body weight decreased ~30% less ($P = 0.05$ vs. PBS) and hair regrowth after shaving was more robust ($P < 0.05$ vs. PBS). Serum biomarkers of inflammation (IL-10, IL-1b, and IL-6) improved in the CDC group ($P < 0.05$ for each, all vs. PBS). Young CDCs secrete exosomes which increase telomerase activity, elongate telomere length, and reduce the number of senescent human heart cells in culture.

Conclusion

Young CDCs rejuvenate old animals as gauged by cardiac gene expression, heart function, exercise capacity, and systemic biomarkers.

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J Biol Chem. 2017 Aug 24. pii: jbc.R117.789271. doi: 10.1074/jbc.R117.789271. [Epub ahead of print]

Production of superoxide and hydrogen peroxide from specific mitochondrial sites under different bioenergetic conditions.

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⊕ Author information

Abstract

Mitochondrial production of superoxide and hydrogen peroxide is potentially important in cell signaling and disease. Eleven distinct mitochondrial sites that differ markedly in capacity are known to leak electrons to oxygen to produce $O_2^{\cdot-}$ and/or H_2O_2 We discuss their contributions to $O_2^{\cdot-}/H_2O_2$ production under native conditions in mitochondria oxidizing different substrates and in conditions mimicking physical exercise, and the changes in their capacities after caloric restriction. We review the use of S1QELs and S3QELs, suppressors of mitochondrial $O_2^{\cdot-}/H_2O_2$ generation that do not inhibit oxidative phosphorylation, as tools to characterize the contributions of specific sites *in situ* and *in vivo*.

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A multimethod computational simulation approach for investigating mitochondrial dynamics and dysfunction in degenerative aging

Research in biogerontology has largely focused on the complex relationship between mitochondrial dysfunction and biological aging. In particular, the mitochondrial free radical theory of aging (MFRTA) has been well accepted. However, this theory has been challenged by recent studies showing minimal increases in reactive oxygen species (ROS) as not entirely deleterious in nature, and even beneficial under the appropriate cellular circumstances. To assess these significant and nonintuitive observations in the context of a functional system, we have taken an *in silico* approach to expand the focus of the MFRTA by including other key mitochondrial stress response pathways, as they have been observed in the nematode *Caenorhabditis elegans*. These include the mitochondrial unfolded protein response (UPR^{mt}), mitochondrial biogenesis and autophagy dynamics, the relevant DAF-16 and SKN-1 axes, and NAD^+-dependent deacetylase activities. To integrate these pathways, we have developed a multilevel hybrid-modeling paradigm, containing agent-based elements among stochastic system-dynamics environments of logically derived ordinary differential equations, to simulate aging mitochondrial phenotypes within a population of energetically demanding cells. The simulation experiments resulted in accurate predictions of physiological parameters over time that accompany normal aging, such as the declines in both NAD^+ and ATP and an increase in ROS. Additionally, the *in silico* system was virtually perturbed using a variety of pharmacological (e.g., rapamycin, pterostilbene, paraquat) and genetic (e.g., *skn-1*, *daf-16, sod-2*) schemes to quantitate the temporal alterations of specific mechanistic targets, supporting insights into molecular determinants of aging as well as cytoprotective agents that may improve neurological or muscular healthspan.

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Ageing Res Rev. 2017 Aug 10;40:31-44. doi: 10.1016/j.arr.2017.08.003. [Epub ahead of print]

Metformin reduces all-cause mortality and diseases of ageing independent of its effect on diabetes control: A systematic review and meta-analysis.

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Author information

Abstract

This systematic review investigated whether the insulin sensitiser metformin has a geroprotective effect in humans. Pubmed and Embase were searched along with databases of unpublished studies. Eligible research investigated the effect of metformin on all-cause mortality or diseases of ageing relative to non-diabetic populations or diabetics receiving other therapies with adjustment for disease control achieved. Overall, 260 full-texts were reviewed and 53 met the inclusion criteria. Diabetics taking metformin had significantly lower all-cause mortality than non-diabetics (hazard ratio (HR)=0.93, 95%CI 0.88-0.99), as did diabetics taking metformin compared to diabetics receiving non-metformin therapies (HR=0.72, 95%CI 0.65-0.80), insulin (HR=0.68, 95%CI 0.63-0.75) or sulphonylurea (HR=0.80, 95%CI 0.66-0.97). Metformin users also had reduced cancer compared to non-diabetics (rate ratio=0.94, 95%CI 0.92-0.97) and cardiovascular disease (CVD) compared to diabetics receiving non-metformin therapies (HR=0.76, 95%CI 0.66-0.87) or insulin (HR=0.78, 95%CI 0.73-0.83). Differences in baseline characteristics were observed which had the potential to bias findings, although statistical adjustments were made. The apparent reductions in all-cause mortality and diseases of ageing associated with metformin use suggest that metformin could be extending life and healthspans by acting as a geroprotective agent.

Int J Cancer. 2017 Aug 25. doi: 10.1002/ijc.31016. [Epub ahead of print]

Risk of cause-specific death in individuals with cancer - modifying role diabetes, statins, and metformin.

Haukka J[1], Niskanen L[2], Auvinen A[3].

Author information

Abstract

Both diabetes mellitus (DM) and cancer are common diseases and they frequently occur in the same patients. We investigated the all-cause and cause-specific mortality dynamics in relation to baseline DM, statin use, and metformin use. The study population consisted of 39,900 incident cancer cases from Finland, 19,822 patients were free of DM at the start of follow-up, and 20,078 had DM. Mortality from all causes, and cancer, cardiovascular (CVD) and other causes was analysed using Poisson regression model with the following variables: sex, age, DM, statin and metformin usage in baseline, cancer type and stage, and calendar period. Statin usage was associated with a reduced cancer-specific mortality with incidence rate ratio (IRR) 0.72 (95% confidence interval 0.69-0.74), IRR for CVD mortality was 0.95 (0.88-1.02), and for other causes 0.64 (0.56-0.74). In a sub-population of DM patients, IRR for metformin in all-cause mortality was 0.74 (0.71-0.78), in cancer mortality 0.75 (0.72-0.79), in CVD mortality 0.75 (0.68-0.83), and other causes 0.68 (0.60-0.78). In conclusion, our register-based study of survival after cancer diagnosis showed that patients with diabetes had substantially poorer outcome in all measures. An association between baseline statin usage and lower all-cause, cancer, and cardiovascular mortality was modified by cancer type. The effect of statin use was largest for breast and colorectal cancer. Metformin usage in a subpopulation of oral antidiabetic users was in general associated with lower mortality, but this association was modified by cancer type. The association was strongest for liver, colorectal, and breast cancer. This article is protected by copyright. All rights reserved.

Loss of Brain Aerobic Glycolysis in Normal Human Aging

The normal aging human brain experiences global decreases in metabolism, but whether this affects the topography of brain metabolism is unknown. Here we describe PET-based measurements of brain glucose uptake, oxygen utilization, and blood flow in cognitively normal adults from 20 to 82 years of age. Age-related decreases in brain glucose uptake exceed that of oxygen use, resulting in loss of brain aerobic glycolysis (AG). Whereas the topographies of total brain glucose uptake, oxygen utilization, and blood flow remain largely stable with age, brain AG topography changes significantly. Brain regions with high AG in young adults show the greatest change, as do regions with prolonged developmental transcriptional features (i.e., neoteny). The normal aging human brain thus undergoes characteristic metabolic changes, largely driven by global loss and topographic changes in brain AG.

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Aged chimpanzees exhibit pathologic hallmarks of Alzheimer's disease

Highlights

- Comparative studies assessing neuropathology between humans and apes are rare.
- This study demonstrates AD-like pathology in a large group of aged chimpanzees.
- Tau lesions include neurofibrillary tangles and tau neuritic clusters.
- Vascular amyloid was associated with tau lesions in the chimpanzee brain.
- Coexistence of both lesions indicates that AD pathology is not limited to humans.

Abstract

Alzheimer's disease (AD) is a uniquely human brain disorder characterized by the accumulation of amyloid beta protein (Aβ) into extracellular plaques, neurofibrillary tangles (NFT) made from intracellular, abnormally phosphorylated tau, and selective neuronal loss. We analyzed a large group of aged chimpanzees (n = 20, ages 37-62 years) for evidence of Aβ and tau lesions in brain regions affected by AD in humans. Aβ was observed in plaques and blood vessels, and tau lesions were found in the form of pretangles, NFT, and tau-immunoreactive neuritic clusters. Aβ deposition was higher in vessels than in plaques and correlated with increases in tau lesions, suggesting that amyloid build-up in the brain's microvasculature precedes plaque formation in chimpanzees. Age was correlated to greater volumes of Aβ plaques and vessels. Tangle pathology was observed in individuals that exhibited plaques and moderate or severe cerebral amyloid angiopathy, a condition in which amyloid accumulates in the brain's vasculature. Amyloid and tau pathology in aged chimpanzees suggests these AD lesions are not specific to the human brain.

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Association of Lithium in Drinking Water With the Incidence of Dementia

Main Outcomes and Measures A diagnosis of dementia in a hospital inpatient or outpatient contact. Diagnoses of Alzheimer disease and vascular dementia were secondary outcome measures. In primary analyses, distribution of lithium exposure was compared between patients with dementia and controls.

Results A total of 73 731 patients with dementia and 733 653 controls (median age, 80.3 years; interquartile range, 74.9-84.6 years; 44 760 female [60.7%] and 28 971 male [39.3%]) were included in the study. Lithium exposure was statistically significantly different between patients with a diagnosis of dementia (median, 11.5 µg/L; interquartile range, 6.5-14.9 µg/L) and controls (median, 12.2 µg/L; interquartile range, 7.3-16.0 µg/L; $P < .001$). A nonlinear association was observed. Compared with individuals exposed to 2.0 to 5.0 µg/L, the incidence rate ratio (IRR) of dementia was decreased in those exposed to more than 15.0 µg/L (IRR, 0.83; 95% CI, 0.81-0.85; $P < .001$) and 10.1 to 15.0 µg/L (IRR, 0.98; 95% CI, 0.96-1.01; $P = .17$) and increased with 5.1 to 10.0 µg/L (IRR, 1.22; 95% CI, 1.19-1.25; $P < .001$). Similar patterns were found with Alzheimer disease and vascular dementia as outcomes.

Conclusions and Relevance Long-term increased lithium exposure in drinking water may be associated with a lower incidence of dementia in a nonlinear way; however, confounding from other factors associated with municipality of residence cannot be excluded.

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Peptidomimetics That Inhibit and Partially Reverse the Aggregation of $A\beta_{1-42}$

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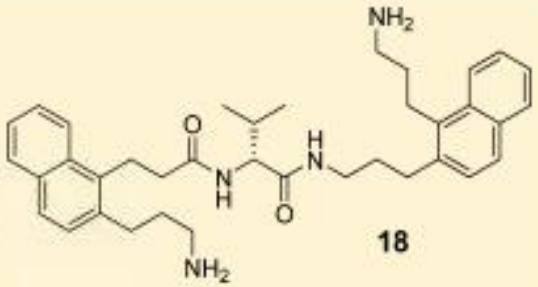
Supporting Information

ABSTRACT: The peptide sequence KLVFF resembles the hydrophobic core of the $A\beta$ peptide known to form amyloid plaques in Alzheimer's disease. Starting from its retro-inverso peptide, we have synthesized three generations of peptidomimetics. Step by step natural amino acids have been replaced by aromatic building blocks accessible from the Pd-catalyzed Catellani reaction. The final compound **18** is stable against proteolytic decay and largely prevents the aggregation of $A\beta_{1-42}$ over extended periods of time. The activity of the new inhibitors was tested first by fluorescence correlation spectroscopy. For closer examination of compound **18**, additional techniques were also applied: laser-induced liquid bead ion desorption mass spectrometry, confocal laser scanning microscopy, thioflavin T fluorescence, and gel electrophoresis. Compound **18** not only retards the aggregation of chemically synthesized $A\beta$ but also can partially dissolve the oligomeric structures. Thioflavin binding mature fibrils, however, seem to resist the inhibitor.



18

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TREM2 Maintains Microglial Metabolic Fitness in Alzheimer's Disease

Highlights

- TREM2-deficient microglia undergo increased autophagy in an AD mouse model
- Microglia in humans with AD-risk-associated *TREM2* alleles display marked autophagy
- TREM2 deficiency impairs microglial mTOR activation and metabolism
- Cyclocreatine improves microglia metabolism and pathology in TREM2-deficient AD mice

Summary

Elevated risk of developing Alzheimer's disease (AD) is associated with hypomorphic variants of TREM2, a surface receptor required for microglial responses to neurodegeneration, including proliferation, survival, clustering, and phagocytosis. How TREM2 promotes such diverse responses is unknown. Here, we find that microglia in AD patients carrying TREM2 risk variants and TREM2-deficient mice with AD-like pathology have abundant autophagic vesicles, as do TREM2-deficient macrophages under growth-factor limitation or endoplasmic reticulum (ER) stress. Combined metabolomics and RNA sequencing (RNA-seq) linked this anomalous autophagy to defective mammalian target of rapamycin (mTOR) signaling, which affects ATP levels and biosynthetic pathways. Metabolic derailment and autophagy were offset in vitro through Dectin-1, a receptor that elicits TREM2-like intracellular signals, and cyclocreatine, a creatine analog that can supply ATP. Dietary cyclocreatine tempered autophagy, restored microglial clustering around plaques, and decreased plaque-adjacent neuronal dystrophy in TREM2-deficient mice with amyloid-β pathology. Thus, TREM2 enables microglial responses during AD by sustaining cellular energetic and biosynthetic metabolism.

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Identification of the Tau phosphorylation pattern that drives its aggregation

Determining the functional relationship between Tau phosphorylation and aggregation has proven a challenge owing to the multiple potential phosphorylation sites and their clustering in the Tau sequence. We use here in vitro kinase assays combined with NMR spectroscopy as an analytical tool to generate well-characterized phosphorylated Tau samples and show that the combined phosphorylation at the Ser202/Thr205/Ser208 sites, together with absence of phosphorylation at the Ser262 site, yields a Tau sample that readily forms fibers, as observed by thioflavin T fluorescence and electron microscopy. On the basis of conformational analysis of synthetic phosphorylated peptides, we show that aggregation of the samples correlates with destabilization of the turn-like structure defined by phosphorylation of Ser202/Thr205.

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Every-other-day feeding extends lifespan but fails to delay many symptoms of aging in mice

Dietary restriction regimes extend lifespan in various animal models. Here we show that longevity in male C57BL/6J mice subjected to every-other-day feeding is associated with a delayed onset of neoplastic disease that naturally limits lifespan in these animals. We compare more than 200 phenotypes in over 20 tissues in aged animals fed with a lifelong every-other-day feeding or ad libitum access to food diet to determine whether molecular, cellular, physiological and histopathological aging features develop more slowly in every-other-day feeding mice than in controls. We also analyze the effects of every-other-day feeding on young mice on shorter-term every-other-day feeding or ad libitum to account for possible aging-independent restriction effects. Our large-scale analysis reveals overall only limited evidence for a retardation of the aging rate in every-other-day feeding mice. The data indicate that every-other-day feeding-induced longevity is sufficiently explained by delays in life-limiting neoplastic disorders and is not associated with a more general slowing of the aging process in mice.

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Circadian Reprogramming in the Liver Identifies Metabolic Pathways of Aging

Highlights

- Aging reprograms clockwork with distinct modalities in the liver versus stem cells
- Liver circadian genomic signatures of aging are reverted by caloric restriction (CR)
- Cyclic protein acetylation is lost in old mice while CR results in hyperacetylation
- CR reorganizes circadian metabolic pathway linked to NAD^+-SIRT1-AceCS1 in the liver

Summary

The process of aging and circadian rhythms are intimately intertwined, but how peripheral clocks involved in metabolic homeostasis contribute to aging remains unknown. Importantly, caloric restriction (CR) extends lifespan in several organisms and rewires circadian metabolism. Using young versus old mice, fed ad libitum or under CR, we reveal reprogramming of the circadian transcriptome in the liver. These age-dependent changes occur in a highly tissue-specific manner, as demonstrated by comparing circadian gene expression in the liver versus epidermal and skeletal muscle stem cells. Moreover, de novo oscillating genes under CR show an enrichment in SIRT1 targets in the liver. This is accompanied by distinct circadian hepatic signatures in NAD^+-related metabolites and cyclic global protein acetylation. Strikingly, this oscillation in acetylation is absent in old mice while CR robustly rescues global protein acetylation. Our findings indicate that the clock operates at the crossroad between protein acetylation, liver metabolism, and aging.

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Aged Stem Cells Reprogram Their Daily Rhythmic Functions to Adapt to Stress

Highlights

- Tissue stem cells retain a rhythmic circadian machinery during aging
- Daily rhythms are reprogrammed in aged SCs to cope with tissue-specific stress
- Rewiring of daily rhythms in aged SCs is prevented by caloric restriction
- Deletion of core clock genes does not recapitulate age-related reprogramming

Summary

Normal homeostatic functions of adult stem cells have rhythmic daily oscillations that are believed to become arrhythmic during aging. Unexpectedly, we find that aged mice remain behaviorally circadian and that their epidermal and muscle stem cells retain a robustly rhythmic core circadian machinery. However, the oscillating transcriptome is extensively reprogrammed in aged stem cells, switching from genes involved in homeostasis to those involved in tissue-specific stresses, such as DNA damage or inefficient autophagy. Importantly, deletion of circadian clock components did not reproduce the hallmarks of this reprogramming, underscoring that rewiring, rather than arrhythmia, is associated with physiological aging. While age-associated rewiring of the oscillatory diurnal transcriptome is not recapitulated by a high-fat diet in young adult mice, it is significantly prevented by long-term caloric restriction in aged mice. Thus, stem cells rewire their diurnal timed functions to adapt to metabolic cues and to tissue-specific age-related traits.

REVIEWS/COMMENTS/EDITORIALS

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SnapShot: Cellular Senescence Pathways

Ricardo Iván Martínez-Zamudio, Lucas Robinson, Pierre-Francois Roux, Oliver Bischof

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Cellular senescence is a fundamental cell fate, playing important physiological and pathophysiological roles. This SnapShot focuses on major signaling pathways and transcriptional control mechanisms that consolidate the senescence phenotype.

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SnapShot: Cellular Senescence in Pathophysiology

Ricardo Iván Martínez-Zamudio, Lucas Robinson, Pierre-François Roux, Oliver Bischof

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https://doi.org/10.1016/j.cell.2017.08.025

Cellular senescence is a fundamental cell fate, important both in physiological and pathophysiological processes. This SnapShot focuses on the role of cellular senescence in health, disease, and aging.

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Kidney Int. 2017 Sep;92(3):569-579. doi: 10.1016/j.kint.2017.02.036. Epub 2017 Jul 18.

Molecular mechanisms of renal aging.

Schmitt R[1], Melk A[2].

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Abstract

Epidemiologic, clinical, and molecular evidence suggest that aging is a major contributor to the increasing incidence of acute kidney injury and chronic kidney disease. The aging kidney undergoes complex changes that predispose to renal pathology. The underlying molecular mechanisms could be the target of therapeutic strategies in the future. Here, we summarize recent insight into cellular and molecular processes that have been shown to contribute to the renal aging phenotype.The main clinical finding of renal aging is the decrease in glomerular filtration rate, and its structural correlate is the loss of functioning nephrons. Mechanistically, this has been linked to different processes, such as podocyte hypertrophy, glomerulosclerosis, tubular atrophy, and gradual microvascular rarefaction. Renal functional recovery after an episode of acute kidney injury is significantly worse in elderly patients. This decreased regenerative potential, which is a hallmark of the aging process, may be caused by cellular senescence. Accumulation of senescent cells could explain insufficient repair and functional loss, a view that has been strengthened by recent studies showing that removal of senescent cells results in attenuation of renal aging. Other potential mechanisms are alterations in autophagy as an important component of a disturbed renal stress response and functional differences in the inflammatory system. Promising therapeutic measures to counteract these age-related problems include mimetics of caloric restriction, pharmacologic renin-angiotensin-aldosterone system inhibition, and novel strategies of senotherapy with the goal of reducing the number of senescent cells to decrease aging-related disease in the kidney.

KEYWORDS: acute kidney injury; cell survival; chronic kidney disease; geriatric nephrology

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High-Definition Medicine

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The foundation for a new era of data-driven medicine has been set by recent technological advances that enable the assessment and management of human health at an unprecedented level of resolution—what we refer to as high-definition medicine. Our ability to assess human health in high definition is enabled, in part, by advances in DNA sequencing, physiological and environmental monitoring, advanced imaging, and behavioral tracking. Our ability to understand and act upon these observations at equally high precision is driven by advances in genome editing, cellular reprogramming, tissue engineering, and information technologies, especially artificial intelligence. In this review, we will examine the core disciplines that enable high-definition medicine and project how these technologies will alter the future of medicine.

OTHER RESEARCH

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Mammals divert endogenous genotoxic formaldehyde into one-carbon metabolism

The folate-driven one-carbon (1C) cycle is a fundamental metabolic hub in cells that enables the synthesis of nucleotides and amino acids and epigenetic modifications. This cycle might also release formaldehyde, a potent protein and DNA crosslinking agent that organisms produce in substantial quantities. Here we show that supplementation with tetrahydrofolate, the essential cofactor of this cycle, and other oxidation-prone folate derivatives kills human, mouse and chicken cells that cannot detoxify formaldehyde or that lack DNA crosslink repair. Notably, formaldehyde is generated from oxidative decomposition of the folate backbone. Furthermore, we find that formaldehyde detoxification in human cells generates formate, and thereby promotes nucleotide synthesis. This supply of 1C units is sufficient to sustain the growth of cells that are unable to use serine, which is the predominant source of 1C units. These findings identify an unexpected source of formaldehyde and, more generally, indicate that the detoxification of this ubiquitous endogenous genotoxin creates a benign 1C unit that can sustain essential metabolism.

Correction of a pathogenic gene mutation in human embryos

Genome editing has potential for the targeted correction of germline mutations. Here we describe the correction of the heterozygous *MYBPC3* mutation in human preimplantation embryos with precise CRISPR–Cas9-based targeting accuracy and high homology-directed repair efficiency by activating an endogenous, germline-specific DNA repair response. Induced double-strand breaks (DSBs) at the mutant paternal allele were predominantly repaired using the homologous wild-type maternal gene instead of a synthetic DNA template. By modulating the cell cycle stage at which the DSB was induced, we were able to avoid mosaicism in cleaving embryos and achieve a high yield of homozygous embryos carrying the wild-type *MYBPC3* gene without evidence of off-target mutations. The efficiency, accuracy and safety of the approach presented suggest that it has potential to be used for the correction of heritable mutations in human embryos by complementing preimplantation genetic diagnosis. However, much remains to be considered before clinical applications, including the reproducibility of the technique with other heterozygous mutations.

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A pathology atlas of the human cancer transcriptome

Recent initiatives such as The Cancer Genome Atlas have mapped the genome-wide effect of individual genes on tumor growth. By unraveling genomic alterations in tumors, molecular subtypes of cancers have been identified, which is improving patient diagnostics and treatment. Uhlen *et al.* developed a computer-based modeling approach to examine different cancer types in nearly 8000 patients. They provide an open-access resource for exploring how the expression of specific genes influences patient survival in 17 different types of cancer. More than 900,000 patient survival profiles are available, including for tumors of colon, prostate, lung, and breast origin. This interactive data set can also be used to generate personalized patient models to predict how metabolic changes can influence tumor growth.