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Human embryonic stem cell-derived retinal pigment epithelium in patients with age-related macular degeneration and Stargardt's macular dystrophy: follow-up of two open-label phase 1/2 studies

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Summary

Background

Since they were first derived more than three decades ago, embryonic stem cells have been proposed as a source of replacement cells in regenerative medicine, but their plasticity and unlimited capacity for self-renewal raises concerns about their safety, including tumour formation ability, potential immune rejection, and the risk of differentiating into unwanted cell types. We report the medium-term to long-term safety of cells derived from human embryonic stem cells (hESC) transplanted into patients.

Methods

In the USA, two prospective phase 1/2 studies were done to assess the primary endpoints safety and tolerability of subretinal transplantation of hESC-derived retinal pigment epithelium in nine patients with Stargardt's macular dystrophy (age >18 years) and nine with atrophic age-related macular degeneration (age >55 years). Three dose cohorts (50 000, 100 000, and 150 000 cells) were treated for each eye disorder. Transplanted patients were followed up for a median of 22 months by use of serial systemic, ophthalmic, and imaging examinations. The studies are registered with ClinicalTrials.gov, numbers NCT01345006 (Stargardt's macular dystrophy) and NCT01344993 (age-related macular degeneration).

Findings

There was no evidence of adverse proliferation, rejection, or serious ocular or systemic safety issues related to the transplanted tissue. Adverse events were associated with vitreoretinal surgery and immunosuppression. 13 (72%) of 18 patients had patches of increasing subretinal pigmentation consistent with transplanted retinal pigment epithelium. Best-corrected visual acuity, monitored as part of the safety protocol, improved in ten eyes, improved or remained the same in seven eyes, and decreased by more than ten letters in one eye, whereas the untreated fellow eyes did not show similar improvements in visual acuity. Vision-related quality-of-life measures increased for general and peripheral vision, and near and distance activities, improving by 16—25 points 3—12 months after transplantation in patients with atrophic age-related macular degeneration and 8—20 points in patients with Stargardt's macular dystrophy.

Interpretation

The results of this study provide the first evidence of the medium-term to long-term safety, graft survival, and possible biological activity of pluripotent stem cell progeny in individuals with any disease. Our results suggest that hESC-derived cells could provide a potentially safe new source of cells for the treatment of various unmet medical disorders requiring tissue repair or replacement.

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Gene Editing of *CCR5* in Autologous CD4 T Cells of Persons Infected with HIV

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N Engl J Med 2014; 370:901-910 | March 6, 2014 | DOI: 10.1056/NEJMoa1300662

METHODS

We enrolled 12 patients in an open-label, nonrandomized, uncontrolled study of a single dose of ZFN-modified autologous CD4 T cells. The patients had chronic aviremic HIV infection while they were receiving highly active antiretroviral therapy. Six of them underwent an interruption in antiretroviral treatment 4 weeks after the infusion of 10 billion autologous CD4 T cells, 11 to 28% of which were genetically modified with the ZFN. The primary outcome was safety as assessed by treatment-related adverse events. Secondary outcomes included measures of immune reconstitution and HIV resistance.

Full Text of Methods...

RESULTS

One serious adverse event was associated with infusion of the ZFN-modified autologous CD4 T cells and was attributed to a transfusion reaction. The median CD4 T-cell count was 1517 per cubic millimeter at week 1, a significant increase from the preinfusion count of 448 per cubic millimeter ($P<0.001$). The median concentration of *CCR5*-modified CD4 T cells at 1 week was 250 cells per cubic millimeter. This constituted 8.8% of circulating peripheral-blood mononuclear cells and 13.9% of circulating CD4 T cells. Modified cells had an estimated mean half-life of 48 weeks. During treatment interruption and the resultant viremia, the decline in circulating *CCR5*-modified cells (−1.81 cells per day) was significantly less than the decline in unmodified cells (−7.25 cells per day) ($P=0.02$). HIV RNA became undetectable in one of four patients who could be evaluated. The blood level of HIV DNA decreased in most patients.

NOT ABOUT AGING BUT THIS STUDY ILLUSTRATES SIGNIFICANT TECHNICAL ADVANCES (MAKING GENETIC CHANGES TO A SPECIFIC LOCATION IN THE GENOME) THAT WILL CERTAINLY BE IMPORTANT IN FUTURE LONGEVITY THERAPIES.

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Single-Walled Carbon Nanotubes Alleviate Autophagic/Lysosomal Defects in Primary Glia from a Mouse Model of Alzheimer's Disease

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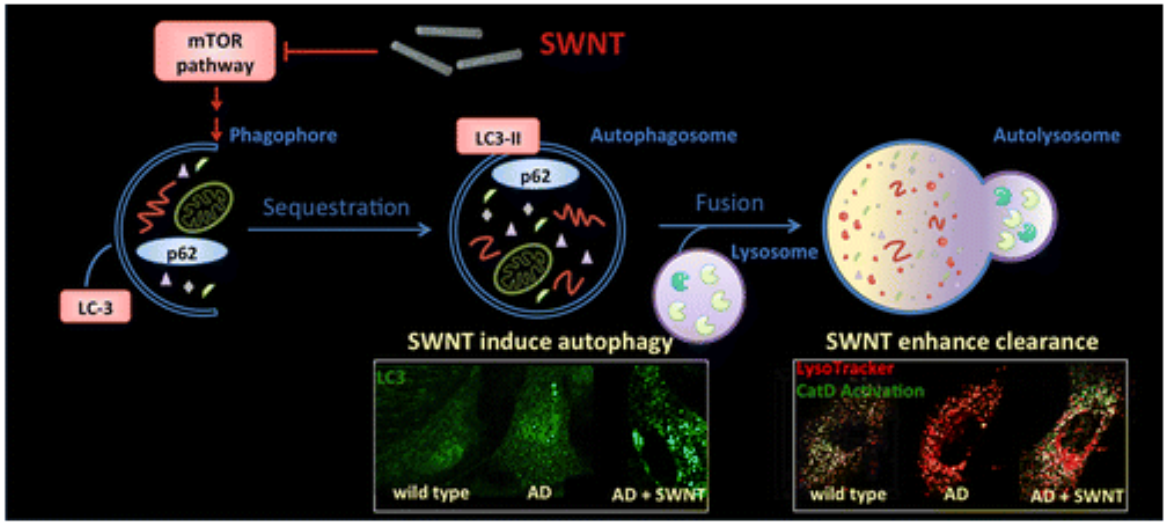

Defective autophagy in Alzheimer's disease (AD) promotes disease progression in diverse ways. Here, we demonstrate impaired autophagy flux in primary glial cells derived from CRND8 mice that overexpress mutant amyloid precursor protein (APP). Functionalized single-walled carbon nanotubes (SWNT) restored normal autophagy by reversing abnormal activation of mTOR signaling and deficits in lysosomal proteolysis, thereby facilitating elimination of autophagic substrates. These findings suggest SWNT as a novel neuroprotective approach to AD therapy.

Keywords: **Single-walled carbon nanotubes**; **primary glia**; **autophagy**; **Alzheimer's disease**

Perinatal Complications and Aging Indicators by Midlife

abstract

BACKGROUND: Perinatal complications predict increased risk for morbidity and early mortality. Evidence of perinatal programming of adult mortality raises the question of what mechanisms embed this long-term effect. We tested a hypothesis related to the theory of developmental origins of health and disease: that perinatal complications assessed at birth predict indicators of accelerated aging by midlife.

METHODS: Perinatal complications, including both maternal and neonatal complications, were assessed in the Dunedin Multidisciplinary Health and Development Study cohort ($N = 1037$), a 38-year, prospective longitudinal study of a representative birth cohort. Two aging indicators were assessed at age 38 years, objectively by leukocyte telomere length (TL) and subjectively by perceived facial age.

RESULTS: Perinatal complications predicted both leukocyte TL ($\beta = -0.101$; 95% confidence interval, −0.169 to −0.033; $P = .004$) and perceived age ($\beta = 0.097$; 95% confidence interval, 0.029 to 0.165; $P = .005$) by midlife. We repeated analyses with controls for measures of family history and social risk that could predispose to perinatal complications and accelerated aging, and for measures of poor health taken in between birth and the age-38 follow-up. These covariates attenuated, but did not fully explain the associations observed between perinatal complications and aging indicators.

CONCLUSIONS: Our findings provide support for early-life developmental programming by linking newborns' perinatal complications to accelerated aging at midlife. We observed indications of accelerated aging "inside," as measured by leukocyte TL, an indicator of cellular aging, and "outside," as measured by perceived age, an indicator of declining tissue integrity. A better understanding of mechanisms underlying perinatal programming of adult aging is needed. *Pediatrics* 2014;134:e1315–e1323

Am J Physiol Regul Integr Comp Physiol. 2014 Aug 15;307(4):R434-43. doi: 10.1152/ajpregu.00123.2014. Epub 2014 Jun 25.

Chronic rapamycin treatment causes diabetes in male mice.

Schindler CE[1], Partap U[1], Patchen BK[1], Swoap SJ[2].

Author information

Abstract

Current evidence indicates that the mammalian target of rapamycin inhibitor rapamycin both increases longevity and, seemingly contradictorily, impairs glucose homeostasis. Most studies exploring the dimensions of this paradox have been based on rapamycin treatment in mice for up to 20 wk. We sought to better understand the metabolic effects of oral rapamycin over a substantially longer period of time in HET3 mice. We observed that treatment with rapamycin for 52 wk induced diabetes in male mice, characterized by hyperglycemia, significant urine glucose levels, and severe glucose and pyruvate intolerance. Glucose intolerance occurred in male mice by 4 wk on rapamycin and could be only partially reversed with cessation of rapamycin treatment. Female mice developed moderate glucose intolerance over 1 yr of rapamycin treatment, but not diabetes. The role of sex hormones in the differential development of diabetic symptoms in male and female mice was further explored. HET3 mice treated with rapamycin for 52 wk were gonadectomized and monitored over 10 wk. Castrated male mice remained glucose intolerant, while ovariectomized females developed significant glucose intolerance over the same time period. Subsequent replacement of 17β-estradiol (E2) in ovariectomized females promoted a recovery of glucose tolerance over a 4-wk period, suggesting the protective role of E2 against rapamycin-induced diabetes. These results indicate that 1) oral rapamycin treatment causes diabetes in male mice, 2) the diabetes is partially reversible with cessation of treatment, and 3) E2 plays a protective role against the development of rapamycin-induced diabetes.

KEYWORDS: diabetes; estradiol; hyperglycemia; mammalian target of rapamycin; rapamycin

Biochim Biophys Acta. 2014 Sep;1842(9):1762-9. doi: 10.1016/j.bbadis.2014.06.018. Epub 2014 Jun 23.

Extra-nuclear telomerase reverse transcriptase (TERT) regulates glucose transport in skeletal muscle cells.

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Author information

Abstract

Telomerase reverse transcriptase (TERT) is a key component of the telomerase complex. By lengthening telomeres in DNA strands, TERT increases senescent cell lifespan. Mice that lack TERT age much faster and exhibit age-related conditions such as osteoporosis, diabetes and neurodegeneration. Accelerated telomere shortening in both human and animal models has been documented in conditions associated with insulin resistance, including T2DM. We investigated the role of TERT, in regulating cellular glucose utilisation by using the myoblastoma cell line C2C12, as well as primary mouse and human skeletal muscle cells. Inhibition of TERT expression or activity by using siRNA (100nM) or specific inhibitors (100nM) reduced basal 2-deoxyglucose uptake by ~50%, in all cell types, without altering insulin responsiveness. In contrast, TERT over-expression increased glucose uptake by 3.25-fold. In C2C12 cells TERT protein was mostly localised intracellularly and stimulation of cells with insulin induced translocation to the plasma membrane. Furthermore, co-immunoprecipitation experiments in C2C12 cells showed that TERT was constitutively associated with glucose transporters (GLUTs) 1, 4 and 12 via an insulin insensitive interaction that also did not require intact PI3-K and mTOR pathways. Collectively, these findings identified a novel extra-nuclear function of TERT that regulates an insulin-insensitive pathway involved in glucose uptake in human and mouse skeletal muscle cells.

KEYWORDS: Ageing; Diabetes; Glucose transporter; Insulin; Muscle; TERT

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Interaction Mortality: Senescence May Have Evolved because It Increases Lifespan

Maarten J. Wensink ✉, Tomasz F. Wrycza, Annette Baudisch

Given an extrinsic challenge, an organism may die or not depending on how the threat interacts with the organism's physiological state. To date, such interaction mortality has been only a minor factor in theoretical modeling of senescence. We describe a model of interaction mortality that does not involve specific functions, making only modest assumptions. Our model distinguishes explicitly between the physiological state of an organism and potential extrinsic, age-independent threats. The resulting mortality may change with age, depending on whether the organism's state changes with age. We find that depending on the physiological constraints, any outcome, be it 'no senescence' or 'high rate of senescence', can be found in any environment; that the highest optimal rate of senescence emerges for an intermediate physiological constraint, i.e. intermediate strength of trade-off; and that the optimal rate of senescence as a function of the environment is driven by the way the environment changes the effect of the organism's state on mortality. We conclude that knowledge about the environment, physiology and their interaction is necessary before reasonable predictions about the evolution of senescence can be made.

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Proteomics. 2014 Oct 15. doi: 10.1002/pmic.201400169. [Epub ahead of print]

Investigation of Phosphoproteome in RAGE signaling.

Batkulwar KB[1], Bansode SB, Patil GV, Godbole RK, Kazi RS, Chinnathambi S, Shanmugam D, Kulkarni MJ.

Author information

Abstract

Receptor for Advanced Glycation End products (RAGE) is one of the most important factors implicated in diabetes, cardiovascular diseases, neurodegenerative diseases, and cancer. It is a pattern recognition receptor, by virtue of its ability to interact with multiple ligands; RAGE activates several signal transduction pathways through involvement of various kinases, which phosphorylate their respective substrates. Only few substrates have been known to be phosphorylated in response to activation by RAGE (e.g.NF-κB), however it is possible that these kinases can phosphorylate multiple substrates depending upon their expression and localization, leading to altered cellular responses in different cell types and conditions. One such example, Glycogen synthase kinase 3 beta (GSK3β) which is known to phosphorylate glycogen synthase, acts downstream to RAGE and hyperphosphorylates Microtubule Associated Protein Tau (MAPT) causing neuronal damage. Thus, it is important to understand the role of various RAGE activated kinases and their substrates. Therefore, we have reviewed here the details of RAGE activated kinases in response to different ligands and their respective phosphoproteome. Further, we discuss the analysis of the data mined for known substrates of these kinases from PhosphoSitePlus (http://www.phosphosite.org) database, and the role of some of the important substrates involved in cancer, diabetes, cardiovascular diseases and neurodegenerative diseases. In summary, this review provides information on RAGE activated kinases and their phosphoproteome, which will be helpful in understanding the possible role of RAGE and its ligands in progression of diseases.

J Am Soc Mass Spectrom. 2014 Oct 15. [Epub ahead of print]

Unexpected Crosslinking and Diglycation as Advanced Glycation End-Products from Glyoxal.

Lopez-Clavijo AF[1], Duque-Daza CA, Soulby A, Canelon IR, Barrow M, O'Connor PB.

Author information

Abstract

Glyoxal-derived advanced glycation end-products (AGEs) are formed in physiological systems affecting protein/peptide function and structure. These AGEs are generated during aging and chronic diseases such as diabetes and are considered arginine glycating agents. Thus, the study of glyoxal-derived AGEs in lysine residues and amino acid competition is addressed here using acetylated and non-acetylated undecapeptides, with one arginine and one lysine residue available for glycation. Tandem mass spectrometry results from a Fourier transform ion cyclotron resonance mass spectrometer showed glycated species at both the arginine and lysine residues. One species with the mass addition of 116.01096 Da is formed at the arginine residue. A possible structure is proposed to explain this finding (Nδ-[2-(dihydroxymethyl)-2H,3aH,4H,6aH-[1, 3]dioxolo[5,6-d]imidazolin-5-yl]-L-ornithine-derived AGE). The second species corresponded to intramolecular crosslink involving the lysine residue and its presence is checked with ion-mobility mass spectrometry.

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J Gerontol A Biol Sci Med Sci. 2014 Oct 13. pii: glu177. [Epub ahead of print]

The Influence of Dietary Fat Source on Life Span in Calorie Restricted Mice.

López-Domínguez JA[1], Ramsey JJ[2], Tran D[1], Imai DM[3], Koehne A[3], Laing ST[3], Griffey SM[3], Kim K[4], Taylor SL[4], Hagopian K[1], Villalba JM[5], López-Lluch G[6], Navas P[6], McDonald RB[7].

Author information

Abstract

Calorie restriction (CR) without malnutrition extends life span in several animal models. It has been proposed that a decrease in the amount of polyunsaturated fatty acids (PUFAs), and especially n-3 fatty acids, in membrane phospholipids may contribute to life span extension with CR. Phospholipid PUFAs are sensitive to dietary fatty acid composition, and thus, the purpose of this study was to determine the influence of dietary lipids on life span in CR mice. C57BL/6J mice were assigned to four groups (a 5% CR control group and three 40% CR groups) and fed diets with soybean oil (high in n-6 PUFAs), fish oil (high in n-3 PUFAs), or lard (high in saturated and monounsaturated fatty acids) as the primary lipid source. Life span was increased ($p < .05$) in all CR groups compared to the Control mice. Life span was also increased ($p < .05$) in the CR lard mice compared to animals consuming either the CR fish or soybean oil diets. These results indicate that dietary lipid composition can influence life span in mice on CR, and suggest that a diet containing a low proportion of PUFAs and high proportion of monounsaturated and saturated fats may maximize life span in animals maintained on CR.

A High Dietary Glycemic Index Increases Total Mortality in a Mediterranean Population at High Cardiovascular Risk

Itandehui Castro-Quezada, Almudena Sánchez-Villegas, Ramón Estruch, Jordi Salas-Salvadó, Dolores Corella, Helmut Schröder, Jacqueline Álvarez-Pérez, María Dolores Ruiz-López, Reyes Artacho, Emilio Ros, Mónica Bulló, María-Isabel Covas, Valentina Ruiz-Gutiérrez, [...], on behalf of the PREDIMED Study Investigators, [view all]

Objective

Different types of carbohydrates have diverse glycemic response, thus glycemic index (GI) and glycemic load (GL) are used to assess this variation. The impact of dietary GI and GL in all-cause mortality is unknown. The objective of this study was to estimate the association between dietary GI and GL and risk of all-cause mortality in the PREDIMED study.

Material and Methods

The PREDIMED study is a randomized nutritional intervention trial for primary cardiovascular prevention based on community-dwelling men and women at high risk of cardiovascular disease. Dietary information was collected at baseline and yearly using a validated 137-item food frequency questionnaire (FFQ). We assigned GI values of each item by a 5-step methodology, using the International Tables of GI and GL Values. Deaths were ascertained through contact with families and general practitioners, review of medical records and consultation of the National Death Index. Cox regression models were used to estimate multivariable-adjusted hazard ratios (HR) and their 95% CI for mortality, according to quartiles of energy-adjusted dietary GI/GL. To assess repeated measures of exposure, we updated GI and GL intakes from the yearly FFQs and used Cox models with time-dependent exposures.

Results

We followed 3,583 non-diabetic subjects (4.7 years of follow-up, 123 deaths). As compared to participants in the lowest quartile of baseline dietary GI, those in the highest quartile showed an increased risk of all-cause mortality [HR = 2.15 (95% CI: 1.15–4.04); P for trend = 0.012]. In the repeated-measures analyses using as exposure the yearly updated information on GI, we observed a similar association. Dietary GL was associated with all-cause mortality only when subjects were younger than 75 years.

Conclusions

High dietary GI was positively associated with all-cause mortality in elderly population at high cardiovascular risk.

Reviews

Biochim Biophys Acta. 2014 Oct 11. pii: S0925-4439(14)00311-1. doi: 10.1016/j.bbadis.2014.10.005. [Epub ahead of print]

The molecular targets of Resveratrol.

Kulkarni SS[1], Cantó C[2].

Author information

Abstract

Resveratrol has emerged in recent years as a compound conferring strong protection against metabolic, cardiovascular and other age-related complications, including neurodegeneration and cancer. This has generated the notion that resveratrol treatment acts as a calorie-restriction mimetic, based on the many overlapping health benefits observed upon both interventions in diverse organisms, including yeast, worms, flies and rodents. Though studied for over a decade, the molecular mechanisms governing the therapeutic properties of resveratrol still remain elusive. Elucidating how resveratrol exerts its effects would not only provide new insights in its fundamental biological actions but also new avenues for the design and development of more potent drugs to efficiently manage metabolic disorders. In this review we will cover the most recent advances in the field, with special focus on the metabolic actions of resveratrol and the potential role of SIRT1 and AMPK. This article is part of a Special Issue entitled: Resveratol: Challenges in translating pre-clincial findigns to iproved patient outcomes, guest edited by J. Dyck and P. Schrauwen.

Biochim Biophys Acta. 2014 Oct 10. pii: S1388-1981(14)00209-1. doi: 10.1016/j.bbalip.2014.09.023. [Epub ahead of print]

Lipid signaling in adipose tissue: Connecting inflammation & metabolism.

Masoodi M[1], Kuda O[2], Rossmeisl M[2], Flachs P[2], Kopecky J[3].

Author information

Abstract

Obesity-associated low-grade inflammation of white adipose tissue (WAT) contributes to development of insulin resistance and other disorders. Accumulation of immune cells, especially macrophages, and macrophage polarization from M2 to M1 state, affect intrinsic WAT signaling, namely anti-inflammatory and proinflammatory cytokines, fatty acids (FA), and lipid mediators derived from both n-6 and n-3 long-chain PUFA such as (i) arachidonic acid (AA)-derived eicosanoids and endocannabinoids, and (ii) specialized pro-resolving lipid mediators including resolvins derived from both eicosapentaenoic (EPA) and docosahexaenoic acid (DHA), lipoxins (AA metabolites), protectins and maresins (DHA metabolites). In this respect, potential differences in modulating adipocyte metabolism by various lipid mediators formed by inflammatory M1 macrophages typical of obese state, and non-inflammatory M2 macrophages typical of lean state remain to be established. Studies in mice suggest that (i) transient accumulation of M2 macrophages could be essential for the control of tissue FA levels during activation of lipolysis, (ii) a currently unidentified M2 macrophage-borne signaling molecule(s) could inhibit lipolysis and re-esterification of lipolyzed FA back to triacylglycerols (TAG/FA cycle), and (iii) the egress of M2 macrophages from rebuilt WAT and removal of the negative feedback regulation could allow for a full unmasking of metabolic activities of adipocytes. Thus, M2 macrophages could support remodeling of WAT to a tissue containing metabolically flexible adipocytes endowed with a high capacity of both TAG/FA cycling and oxidative phosphorylation. This situation could be exemplified by a combined intervention using mild calorie restriction and dietary supplementation with EPA/DHA, which enhances the formation of "healthy" adipocytes.

F1000Res. 2014 Sep 12;3:219. doi: 10.12688/f1000research.5212.1. eCollection 2014.

Aging and energetics' 'Top 40' future research opportunities 2010-2013.

Allison DB[1], Antoine LH[2], Ballinger SW[3], Bamman MM[4], Biga P[5], Darley-Usmar VM[6], Fisher G[7], Gohlke JM[8], Halade GV[9], Hartman JL[10], Hunter GR[7], Messina JL[11], Nagy TR[12], Plaisance EP[7], Powell ML[5], Roth KA[5], Sandel MW[13], Schwartz TS[14], Smith DL[15], Sweatt JD[16], Tollefsbol TO[5], Watts SA[5], Yang Y[17], Zhang J[18], Austad SN[19].

⊕ Author information

Abstract

BACKGROUND: As part of a coordinated effort to expand our research activity at the interface of Aging and Energetics a team of investigators at The University of Alabama at Birmingham systematically assayed and catalogued the top research priorities identified in leading publications in that domain, believing the result would be useful to the scientific community at large.

OBJECTIVE: To identify research priorities and opportunities in the domain of aging and energetics as advocated in the 40 most cited papers related to aging and energetics in the last 4 years.

DESIGN: The investigators conducted a search for papers on aging and energetics in Scopus, ranked the resulting papers by number of times they were cited, and selected the ten most-cited papers in each of the four years that include 2010 to 2013, inclusive.

RESULTS: Ten research categories were identified from the 40 papers. These included: (1) Calorie restriction (CR) longevity response, (2) role of mTOR (mechanistic target of Rapamycin) and related factors in lifespan extension, (3) nutrient effects beyond energy (especially resveratrol, omega-3 fatty acids, and selected amino acids), 4) autophagy and increased longevity and health, (5) aging-associated predictors of chronic disease, (6) use and effects of mesenchymal stem cells (MSCs), (7) telomeres relative to aging and energetics, (8) accretion and effects of body fat, (9) the aging heart, and (10) mitochondria, reactive oxygen species, and cellular energetics.

CONCLUSION: The field is rich with exciting opportunities to build upon our existing knowledge about the relations among aspects of aging and aspects of energetics and to better understand the mechanisms which connect them.