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Scientific News 6th of July 2014
Sven Bulterijs

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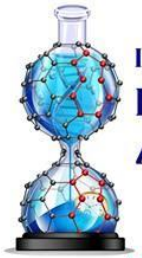
Conferences



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NATURE | EDITORIAL

STAP retracted

Two retractions highlight long-standing issues of trust and sloppiness that must be addressed.

02 July 2014

This week, *Nature* publishes retractions of two high-profile papers that claimed a major advance in the field of stem cells (see page 112). Between them, the two papers seemed to demonstrate that a physical perturbation could do what had previously been achieved only by genetic manipulation:

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THE JOURNAL OF
FAMILY PRACTICE

Caldwell B. Esselstyn Jr, MD; Gina Gendy, MD; Jonathan Doyle, MCS; Mladen Golubic, MD, PhD; Michael F. Roizen, MD
The Wellness Institute of the Cleveland Clinic, Lyndhurst, Ohio

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The authors reported no potential conflict of interest relevant to this article.

ORIGINAL RESEARCH

A way to reverse CAD?

Though current medical and surgical treatments manage coronary artery disease, they do little to prevent or stop it. Nutritional intervention, as shown in our study and others, has halted and even reversed CAD.

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A novel Aβ-fibrinogen interaction inhibitor rescues altered thrombosis and cognitive decline in Alzheimer's disease mice

Hyung Jin Ahn[1], J. Fraser Glickman[2], Ka Lai Poon[1], Daria Zamolodchikov[1], Odella C. Jno-Charles[1], Erin H. Norris[1], and Sidney Strickland[1]

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ABSTRACT

Many Alzheimer's disease (AD) patients suffer from cerebrovascular abnormalities such as altered cerebral blood flow and cerebral microinfarcts. Recently, fibrinogen has been identified as a strong cerebrovascular risk factor in AD, as it specifically binds to β-amyloid (Aβ), thereby altering fibrin clot structure and delaying clot degradation. To determine if the Aβ–fibrinogen interaction could be targeted as a potential new treatment for AD, we designed a high-throughput screen and identified RU-505 as an effective inhibitor of the Aβ–fibrinogen interaction. RU-505 restored Aβ-induced altered fibrin clot formation and degradation in vitro and inhibited vessel occlusion in AD transgenic mice. Furthermore, long-term treatment of RU-505 significantly reduced vascular amyloid deposition and microgliosis in the cortex and improved cognitive impairment in mouse models of AD. Our studies suggest that inhibitors targeting the Aβ–fibrinogen interaction show promise as therapy for treating AD.

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Biochem Biophys Res Commun. 2014 Jun 24. pii: S0006-291X(14)01159-0. doi: 10.1016/j.bbrc.2014.06.085. [Epub ahead of print]

Increased centrosome amplification in aged stem cells of the Drosophila midgut.

Park JS[1], Pyo JH[1], Na HJ[1], Jeon HJ[1], Kim YS[1], Arking R[2], Yoo MA[3].

Author information

Abstract

Age-related changes in long-lived tissue-resident stem cells may be tightly linked to aging and age-related diseases such as cancer. Centrosomes play key roles in cell proliferation, differentiation and migration. Supernumerary centrosomes are known to be an early event in tumorigenesis and senescence. However, the age-related changes of centrosome duplication in tissue-resident stem cells in vivo remain unknown. Here, using anti-γ-tubulin and anti-PH3, we analyzed mitotic intestinal stem cells with supernumerary centrosomes in the adult Drosophila midgut, which may be a versatile model system for stem cell biology. The results showed increased centrosome amplification in intestinal stem cells of aged and oxidatively stressed Drosophila midguts. Increased centrosome amplification was detected by overexpression of PVR, EGFR, and AKT in intestinal stem cells/enteroblasts, known to mimic age-related changes including hyperproliferation of intestinal stem cells and hyperplasia in the midgut. Our data show the first direct evidence for the age-related increase of centrosome amplification in intestinal stem cells and suggest that the Drosophila midgut is an excellent model for studying molecular mechanisms underlying centrosome amplification in aging adult stem cells in vivo.

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Chem Biol Interact. 2014 Jun 23. pii: S0009-2797(14)00191-4. doi: 10.1016/j.cbi.2014.06.012. [Epub ahead of print]

Immunogenicity of DNA-advanced glycation end product fashioned through glyoxal and arginine in the presence of Fe3+: Its potential role in prompt recognition of diabetes mellitus auto-antibodies.

Shahab U[1], Tabrez S[2], Khan MS[2], Akhter F[2], Khan MS[2], Saeed M[2], Ahmad K[2], Srivastava AK[2], Ahmad S[3].

Author information

Abstract

Glyoxal, methylglyoxal and 3-deoxyglucosones are reactive dicarbonyl compounds, which transform free amino groups of proteins and lipoproteins macromolecule into advanced glycation end-products (AGEs). AGEs play a significant role in the pathophysiology of aging and diabetic complications because of their genotoxic effect. Glyoxal also reacts with free amino group of nucleic acids resulting in the formation of DNA-AGEs. The present study reports the genotoxicity and immunogenicity of AGEs formed by Glyoxal-Arginine-Fe^{3+} (G-Arg-Fe^{3+}) system as a glycating agent. Immunogenicity of native and G-Arg-Fe^{3+}-DNA was probed in female rabbits. Immunofluorescence suggests the presence of immune complex deposition in the kidney section of immunized rabbits. Spectroscopic analysis and melting temperature indicates the structural modification in the human DNA. The modified human DNA is found to be highly immunogenic, whereas unmodified form was simply non-immunogenic. This study shows the presence of auto-antibodies against G-Arg-Fe^{3+} modified human DNA in the sera of diabetes type 1 and in few cases type 2 patients due to secondary complications of nephropathy. The glyco-oxidative lesions have also been detected in the lymphocyte DNA isolated from patients having type 1 and type 2 diabetes. The results show structural perturbations generating new epitopes in G-Arg-Fe^{3+}-DNA rendering it pretty immunogenic.

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PLoS One. 2014 Jun 27;9(6):e100562. doi: 10.1371/journal.pone.0100562. eCollection 2014.

Role of metformin in suppressing 1,2-dimethylhydrazine-induced colon cancer in diabetic and non-diabetic mice: effect on tumor angiogenesis and cell proliferation.

Zaafar DK[1], Zaitone SA[2], Moustafa YM[2].

Author information

Abstract

Several studies indicated that type 2 diabetes mellitus and insulin resistance are associated with increased colon cancer risk. Recently, studies suggest that metformin can reduce cancer risk in diabetic or non-diabetic patients with unclear mechanisms. This work aimed to determine the effect of metformin on chemically-induced colon cancer in mice. Colon cancer was induced using 1,2-dimethylhydrazine (DMH, 20 mg/kg/week, s.c.) for fifteen weeks. Experiment I: healthy mice were fed with basal diet for four weeks and then allocated into seven groups, (i) saline, (ii) DMH, (iii) oxaliplatin, (iv-v): metformin (100 or 200 mg/kg) and (vi-vii): oxaliplatin+metformin (100 or 200 mg/kg), respectively. Experiment II: type 2 diabetes mellitus was induced by injection of STZ (30 mg/kg) after four weeks of high-fat feeding and then mice were allocated into seven groups similar to those reported in experiment I. Examination of the colonic tissue at the end of the experiment highlighted an increase in angiogenic markers and cell proliferation and showed a greater immunostaining for insulin growth factor I receptors and CD34 in the colon of diabetic mice compared to non-diabetics. In general, metformin downregulated tumor angiogenesis and augmented the antitumor effect of oxaliplatin. Overall, the current results showed that metformin protected against DMH-induced colon cancer in non-diabetic and diabetic mice. This therapeutic effect was, at least in part, attributed to its anti-angiogenic and anti-proliferative mechanisms.

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BioMed Central blog

The failure rate of clinical trials for Alzheimer's – why we need to raise our game

Guest on July 3, 2014 at 5:00 am - 2 Comments

Dr Simon Ridley of Alzheimer's Research UK

New research published today in *Alzheimer's Research and Therapy* has shown that the failure rate for Alzheimer's Disease drug development is 99.6%. In this guest blog, Dr Simon Ridley, Head of Research at Alzheimer's Research UK, discusses the challenges we are facing in tackling this devastating condition, and what we can do to address them.

Dementia is the name for a collection of many different conditions, of which Alzheimer's disease is the most common. Alzheimer's is characterised by a gradual decline in memory and changes in behaviour and communication. In the later stages, people often forget their friends and family as well as how to walk and feed themselves and require round-the-clock care. Whilst there are some treatments available that can help with the symptoms of Alzheimer's, there is currently no cure.

Current estimates are that 820,000 people in the UK are affected by dementia and the aging population means that this number is expected to rise to over 2 million by 2050. The economic impact of dementia is enormous, costing the UK £23bn a year and £360bn worldwide.

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Age (Dordr). 2014 Aug;36(4):9677. Epub 2014 Jul 5.

Association of exceptional parental longevity and physical function in aging.

Ayers E[1], Barzilai N, Crandall JP, Milman S, Verghese J.

Author information

Abstract

Offspring of parents with exceptional longevity (OPEL), who are more likely to carry longevity-associated genotypes, may age more successfully than offspring of parents with usual survival (OPUS). Maintenance of physical function is a key attribute of successful aging. While many genetic and non-genetic factors interact to determine physical phenotype in aging, examination of the contribution of exceptional parental longevity to physical function in aging is limited. The LonGenity study recruited a relatively genetically homogenous cohort of Ashkenazi Jewish (AJ) adults age 65 and older, who were defined as either OPEL (having at least one parent who lived to age 95 or older) or OPUS (neither parent survived to age 95). Subjective and objective measures of physical function were compared between the two groups, accounting for potential confounders. Of the 893 LonGenity subjects, 365 were OPEL and 528 were OPUS. OPEL had better objective and subjective measures of physical function than OPUS, especially on unipedal stance ($p = 0.009$) and gait speed ($p = 0.002$). Results support the protective role of exceptional parental longevity in preventing decline in physical function, possibly via genetic mechanisms that should be further explored.

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Neurobiol Aging. 2014 Jun 6. pii: S0197-4580(14)00396-0. doi: 10.1016/j.neurobiolaging.2014.05.030. [Epub ahead of print]

Trajectories of inflammatory markers and cognitive decline over 10 years.

Metti AL[1], Yaffe K[2], Boudreau RM[3], Simonsick EM[4], Carnahan RM[5], Satterfield S[6], Harris TB[7], Ayonayon HN[8], Rosano C[3], Cauley JA[3]; Health ABC Study.

Author information

Abstract

We aimed to examine trajectories of inflammatory markers and cognitive decline over 10 years. Cox proportional hazards models were used to examine the association between interleukin-6 and C-reactive protein (CRP) trajectory components (slope, variability, and baseline level) and cognitive decline among 1323 adults, aged 70-79 years in the Health, Aging, and Body Composition Study. We tested for interactions by sex and apolipoprotein E (APOE) genotype. In models adjusted for multiple covariates and comorbidities, extreme CRP variability was significantly associated with cognitive decline (hazard ratio [HR] 1.6, 95% confidence interval [CI]: 1.1-2.3). This association was modified by sex and APOE e4 ($p < 0.001$ for both), such that the association remained among women (HR = 1.8; 95% CI: 1.1, 3.0) and among those with no APOE e4 allele (HR = 1.6; 95% CI: 1.1, 2.5). There were no significant associations between slope or baseline level of CRP and cognitive decline nor between interleukin-6 and cognitive decline. We believe CRP variability likely reflects poor control of or greater changes in vascular or metabolic disease over time, which in turn is associated with cognitive decline.

Reviews

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Comparative genetics of longevity and cancer: insights from long-lived rodents

Vera Gorbunova, Andrei Seluanov, Zhengdong Zhang, Vadim N. Gladyshev & Jan Vijg

Mammals have evolved a remarkable diversity of ageing rates. Within the single order of Rodentia, maximum lifespans range from 4 years in mice to 32 years in naked mole rats. Cancer rates also differ substantially between cancer-prone mice and almost cancer-proof naked mole rats and blind mole rats. Recent progress in rodent comparative biology, together with the emergence of whole-genome sequence information, has opened opportunities for the discovery of genetic factors that control longevity and cancer susceptibility.