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Scientific News 7<sup>th</sup> of June 2015  
Sven Bulterijs





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## OPINION ARTICLE

Front. Genet. | doi: 10.3389/fgene.2015.00205

# It is time to classify biological aging as a disease

 [Sven Bulterijs](#)<sup>1, 2\*</sup>,  [Raphaella S. Hull](#)<sup>3, 4</sup>,  [Victor C. Björk](#)<sup>1, 5</sup> and  [Avi G. Roy](#)<sup>1, 4, 6</sup>

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Article

## GDF11 Increases with Age and Inhibits Skeletal Muscle Regeneration

Marc A. Egerman<sup>1</sup>, Samuel M. Cadena<sup>1</sup>, Jason A. Gilbert<sup>1</sup>, Angelika Meyer<sup>3</sup>, Hallie N. Nelson<sup>2</sup>, Susanne E. Swalley<sup>1</sup>, Carolyn Mallozzi<sup>1</sup>, Carsten Jacobi<sup>3</sup>, Lori L. Jennings<sup>1</sup>, Ieuan Clay<sup>3</sup>, Gaëlle Laurent<sup>1</sup>, Shenglin Ma<sup>1</sup>, Sophie Brachat<sup>3</sup>, Estelle Lach-Trifilieff<sup>3</sup>, Tea Shavlakadze<sup>1</sup>, Anne-Ulrike Trendelenburg<sup>1</sup>, Andrew S. Brack<sup>2,4</sup>, David J. Glass<sup>1</sup>  

### Summary

Age-related frailty may be due to decreased skeletal muscle regeneration. The role of TGF- $\beta$  molecules myostatin and GDF11 in regeneration is unclear. Recent studies showed an age-related decrease in GDF11 and that GDF11 treatment improves muscle regeneration, which were contrary to prior studies. We now show that these recent claims are not reproducible and the reagents previously used to detect GDF11 are not GDF11 specific. We develop a GDF11-specific immunoassay and show a trend toward increased GDF11 levels in sera of aged rats and humans. GDF11 mRNA increases in rat muscle with age. Mechanistically, GDF11 and myostatin both induce SMAD2/3 phosphorylation, inhibit myoblast differentiation, and regulate identical downstream signaling. GDF11 significantly inhibited muscle regeneration and decreased satellite cell expansion in mice. Given early data in humans showing a trend for an age-related increase, GDF11 could be a target for pharmacologic blockade to treat age-related sarcopenia.



# 'Young blood' anti-ageing mechanism called into question

A protein in the blood of young mice that seemed to rejuvenate older animals may do the opposite.

**Sara Reardon**

19 May 2015

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Getty Images

Blood from young animals seems to regenerate muscles in older ones, but researchers have not yet pinned down why.

Short Article

## AMPK Activation of Muscle Autophagy Prevents Fasting-Induced Hypoglycemia and Myopathy during Aging



Adam L. Bujak<sup>1</sup>, Justin D. Crane<sup>1,2</sup>, James S. Lally<sup>1</sup>, Rebecca J. Ford<sup>1</sup>, Sally J. Kang<sup>1</sup>, Irena A. Rebalka<sup>1</sup>, Alex E. Green<sup>1</sup>, Bruce E. Kemp<sup>5</sup>, Thomas J. Hawke<sup>3</sup>, Jonathan D. Schertzer<sup>2,4</sup>, Gregory R. Steinberg<sup>1,4</sup>.  

### Summary

The AMP-activated protein kinase (AMPK) activates autophagy, but its role in aging and fasting-induced muscle function has not been defined. Here we report that fasting mice lacking skeletal muscle AMPK (AMPK-MKO) results in hypoglycemia and hyperketosis. This is not due to defective fatty acid oxidation, but instead is related to a block in muscle proteolysis that leads to reduced circulating levels of alanine, an essential amino acid required for gluconeogenesis. Markers of muscle autophagy including phosphorylation of Ulk1 Ser555 and Ser757 and aggregation of RFP-LC3 puncta are impaired. Consistent with impaired autophagy, aged AMPK-MKO mice possess a significant myopathy characterized by reduced muscle function, mitochondrial disease, and accumulation of the autophagy/mitophagy proteins p62 and Parkin. These findings establish an essential requirement for skeletal muscle AMPK-mediated autophagy in preserving blood glucose levels during prolonged fasting as well as maintaining muscle integrity and mitochondrial function during aging.

Article

## Mosaic Deficiency in Mitochondrial Oxidative Metabolism Promotes Cardiac Arrhythmia during Aging

Olivier R. Baris<sup>1</sup>, Stefan Ederer<sup>1</sup>, Johannes F.G. Neuhaus<sup>1</sup>, Jürgen-Christoph von Kleist-Retzow<sup>2</sup>, Claudia M. Wunderlich<sup>3, 4, 5</sup>, Martin Pal<sup>3, 4, 5</sup>, F. Thomas Wunderlich<sup>3, 4, 5</sup>, Viktoriya Peeva<sup>6</sup>, Gabor Zsurka<sup>6</sup>, Wolfram S. Kunz<sup>6</sup>, Tilman Hickethier<sup>7</sup>, Alexander C. Bunck<sup>7</sup>, Florian Stöckigt<sup>8</sup>, Jan W. Schrickel<sup>8</sup>, Rudolf J. Wiesner<sup>1, 4, 5</sup>.  

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### Summary

Aging is a progressive decline of body function, during which many tissues accumulate few cells with high levels of deleted mitochondrial DNA (mtDNA), leading to a defect of mitochondrial functions. Whether this mosaic mitochondrial deficiency contributes to organ dysfunction is unknown. To investigate this, we generated mice with an accelerated accumulation of mtDNA deletions in the myocardium, by expressing a dominant-negative mutant mitochondrial helicase. These animals accumulated few randomly distributed cardiomyocytes with compromised mitochondrial function, which led to spontaneous ventricular premature contractions and AV blocks at 18 months. These symptoms were not caused by a general mitochondrial dysfunction in the entire myocardium, and were not observed in mice at 12 months with significantly lower numbers of dysfunctional cells. Therefore, our results suggest that the disposition to arrhythmia typically found in the aged human heart might be due to the random accumulation of mtDNA deletions and the subsequent mosaic respiratory chain deficiency.

# Coordination of mitophagy and mitochondrial biogenesis during ageing in *C. elegans*

Konstantinos Palikaras, Eirini Lionaki & Nektarios Tavernarakis

[Affiliations](#) | [Contributions](#) | [Corresponding author](#)

*Nature* **521**, 525–528 (28 May 2015) | doi:10.1038/nature14300

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**Impaired mitochondrial maintenance in disparate cell types is a shared hallmark of many human pathologies and ageing<sup>1, 2, 3, 4, 5, 6, 7, 8</sup>. How mitochondrial biogenesis coordinates with the removal of damaged or superfluous mitochondria to maintain cellular homeostasis is not well understood. Here we show that mitophagy, a selective type of autophagy targeting mitochondria for degradation, interfaces with mitochondrial biogenesis to regulate mitochondrial content and longevity in *Caenorhabditis elegans*. We find that DCT-1 is a key mediator of mitophagy and longevity assurance under conditions of stress in *C. elegans*. Impairment of mitophagy compromises stress resistance and triggers mitochondrial retrograde signalling through the SKN-1 transcription factor that regulates both mitochondrial biogenesis genes and mitophagy by enhancing DCT-1 expression. Our findings reveal a homeostatic feedback loop that integrates metabolic signals to coordinate the biogenesis and turnover of mitochondria. Uncoupling of these two processes during ageing contributes to overproliferation of damaged mitochondria and decline of cellular function.**



# Basal Level of Autophagy Is Increased in Aging Human Skin Fibroblasts *In Vitro*, but Not in Old Skin

Dino Demirovic, Carine Nizard, Suresh I. S. Rattan 

Published: May 7, 2015 • DOI: 10.1371/journal.pone.0126546

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## Abstract

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## Abstract

Intracellular autophagy (AP) is a stress response that is enhanced under conditions of limitation of amino acids, growth factors and other nutrients, and also when macromolecules become damaged, aggregated and fibrillated. Aging is generally accompanied by an increase in intracellular stress due to all the above factors. Therefore, we have compared the basal levels of AP in serially passaged human facial skin fibroblasts undergoing aging and replicative senescence *in vitro*, and *ex vivo* in the skin biopsies from the photo-protected and photo-exposed area of the arms of 20 healthy persons of young and old ages. Immunofluorescence microscopy, employing antibodies against a specific intracellular microtubule-associated protein-1 light chain-3 (LC3) as a well established marker of AP, showed a 5-fold increase in the basal level of LC3 in near senescent human skin fibroblasts. However, no such age-related increase in LC3 fluorescence and AP could be detected in full thickness skin sections from the biopsies obtained from 10 healthy young (age 25 to 30 yr) and 10 old (age 60 to 65 yr) donors. Furthermore, there was no difference in the basal level of LC3 in the skin sections from photo-protected and photo-exposed areas of the arm. Thus, in normal conditions, the aging phenotype of the skin cells in culture and in the body appears to be different in the case of AP.

# Cancer Incidence among Patients with Anorexia Nervosa from Sweden, Denmark and Finland

Lene Mellekjær , Fotios C. Papadopoulos, Eero Pukkala, Anders Ekblom, Mika Gissler, Jane Christensen, Jørgen H. Olsen

Published: May 22, 2015 • DOI: 10.1371/journal.pone.0128018

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## Abstract

A diet with restricted energy content reduces the occurrence of cancer in animal experiments. It is not known if the underlying mechanism also exists in human beings. To determine whether cancer incidence is reduced among patients with anorexia nervosa who tend to have a low intake of energy, we carried out a retrospective cohort study of 22 654 women and 1678 men diagnosed with anorexia nervosa at ages 10-50 years during 1968-2010 according to National Hospital Registers in Sweden, Denmark and Finland. The comparison group consisted of randomly selected persons from population registers who were similar to the anorexia nervosa patients in respect to sex, year of birth and place of residence. Patients and population comparisons were followed for cancer by linkage to Cancer Registries. Incidence rate ratios (IRR) were estimated using Poisson models. In total, 366 cases of cancer (excluding non-melanoma skin cancer) were seen among women with anorexia nervosa, and the IRR for all cancer sites was 0.97 (95% CI = 0.87-1.08) adjusted for age, parity and age at first child. There were 76 breast cancers corresponding to an adjusted IRR of 0.61 (95% CI = 0.49-0.77). Significantly increased IRRs were observed for esophageal, lung, and liver cancer. Among men with anorexia nervosa, there were 23 cases of cancer (age-adjusted IRR = 1.08; 95% CI = 0.71-1.66). There seems to be no general reduction in cancer occurrence among patients with anorexia nervosa, giving little support to the energy restriction hypothesis.

[Invest Ophthalmol Vis Sci](#), 2015 May 1;56(5):2892-7. doi: 10.1167/iovs.14-15840.

## **Advanced glycation end-product accumulation reduces vitreous permeability.**

[Lee OT](#), [Good SD](#), [Lamy R](#), [Kudisch M](#), [Stewart JM](#).

### **Abstract**

**PURPOSE:** To evaluate the effect of nonenzymatic cross-linking (glycation) upon the permeability of the vitreous to small- and large-solute diffusion.

**METHODS:** Vitreous from freshly excised porcine eyes was treated for 30 minutes with control or 0.01%, 0.1%, or 1% methylglyoxal (MG) solution. The efficacy of the glycation regimen was verified by measuring nonenzymatic cross-link density by fluorescence in the vitreous samples. Resistance to collagenase digestion as well as N $\epsilon$ -(carboxyethyl) lysine (CEL) content were also measured. The permeability coefficient for fluorescein and fluorescein isothiocyanate (FITC)-IgG diffusion through 3 mL of the vitreous samples was determined by using a custom permeability tester.

**RESULTS:** Vitreous cross-linking with MG treatment was confirmed by increased fluorescence, increased CEL concentration, and increased resistance to collagenase digestion. Vitreous glycation resulted in a statistically significant decrease in the permeability coefficient for fluorescein diffusion when either 0.1% or 1% MG solution was used ( $5.36 \pm 5.24 \times 10^{-5}$  cm s $^{-1}$ ,  $P = 0.04$ ; and  $4.03 \pm 2.1 \times 10^{-5}$  cm s $^{-1}$ ,  $P = 0.001$ ; respectively, compared with control,  $9.77 \pm 5.45 \times 10^{-5}$  cm s $^{-1}$ ). The permeability coefficient for diffusion of FITC-IgG between control ( $9.9 \pm 6.37 \times 10^{-5}$  cm s $^{-1}$ ) and treatment groups was statistically significant at all MG concentrations (0.01% MG:  $3.95 \pm 3.44 \times 10^{-5}$  cm s $^{-1}$ ,  $P = 0.003$ ; 0.1% MG:  $4.27 \pm 1.32 \times 10^{-5}$  cm s $^{-1}$ ,  $P = 0.004$ ; and 0.1% MG:  $3.72 \pm 2.49 \times 10^{-5}$  cm s $^{-1}$ ,  $P = 0.001$ ).

**CONCLUSIONS:** Advanced glycation end-product (AGE) accumulation reduces vitreous permeability when glycation is performed in ex vivo porcine vitreous. The permeability change was more pronounced for the larger solute, suggesting a lower threshold for AGE-induced permeability changes to impact the movement of proteins through the vitreous when compared with smaller molecules.

[Stem Cells Transl Med.](#) 2015 May 29. pii: sctm.2014-0184. [Epub ahead of print]

## **Bystander Effect Fuels Human Induced Pluripotent Stem Cell-Derived Neural Stem Cells to Quickly Attenuate Early Stage Neurological Deficits After Stroke.**

[Eckert A<sup>1</sup>](#), [Huang L<sup>1</sup>](#), [Gonzalez R<sup>1</sup>](#), [Kim HS<sup>1</sup>](#), [Hamblin MH<sup>1</sup>](#), [Lee JP<sup>2</sup>](#).

### **⊕ Author information**

#### **Abstract**

Present therapies for stroke rest with tissue plasminogen activator (tPA), the sole licensed antithrombotic on the market; however, tPA's effectiveness is limited in that the drug not only must be administered less than 3-5 hours after stroke but often exacerbates blood-brain barrier (BBB) leakage and increases hemorrhagic incidence. A potentially promising therapy for stroke is transplantation of human induced pluripotent stem cell-derived neural stem cells (hiPSC-NSCs). To date, the effects of iPSCs on injuries that take place during early stage ischemic stroke have not been well studied. Consequently, we engrafted iPSC-NSCs into the ipsilesional hippocampus, a natural niche of NSCs, at 24 hours after stroke (prior to secondary BBB opening and when inflammatory signature is abundant). At 48 hours after stroke (24 hours after transplant), hiPSC-NSCs had migrated to the stroke lesion and quickly improved neurological function. Transplanted mice showed reduced expression of proinflammatory factors (tumor necrosis factor- $\alpha$ , interleukin 6 [IL-6], IL-1 $\beta$ , monocyte chemoattractant protein 1, macrophage inflammatory protein 1 $\alpha$ ), microglial activation, and adhesion molecules (intercellular adhesion molecule 1, vascular cell adhesion molecule 1) and attenuated BBB damage. We are the first to report that engrafted hiPSC-NSCs rapidly improved neurological function (less than 24 hours after transplant). Rapid hiPSC-NSC therapeutic activity is mainly due to a bystander effect that elicits reduced inflammation and BBB damage.

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**KEYWORDS:** Blood-brain barrier; Cellular therapy; Induced pluripotent stem cells; Inflammation; Neural stem cell; Stem cell transplantation; Stroke



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