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HEALTHY LIFE EXTENSION SOCIETY

Scientific News
25th of June 2016
Sven Bulterijs

“Latest Aging Research Updates” Facebook group is now public!

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The Japan News
by The Yomiuri Shimbun

NEWS BLOG 読売新聞(Japanese Edition)

TOP | POLITICS | SOCIETY | BUSINESS | WORLD | SPORTS | EDITORIAL | FEATURES

1st clinical trial set for 'anti-aging compound'

8:24 pm, June 21, 2016

The Yomiuri Shimbun

Keio University and Washington University in St. Louis plan to begin a joint clinical study in Japan to test the safety and effectiveness in humans of a compound that is gradually being proved to retard the aging process in animals, scientists have said.

Keio University's Research Ethics Committee will check the appropriateness of the plan and other factors. If approved, researchers plan to begin giving the compound — nicotinamide mononucleotide (see below) or NMN — to about 10 healthy people to confirm its safety. They will then examine whether NMN can improve functions of the human body.

The clinical study is scheduled to begin as early as next month.

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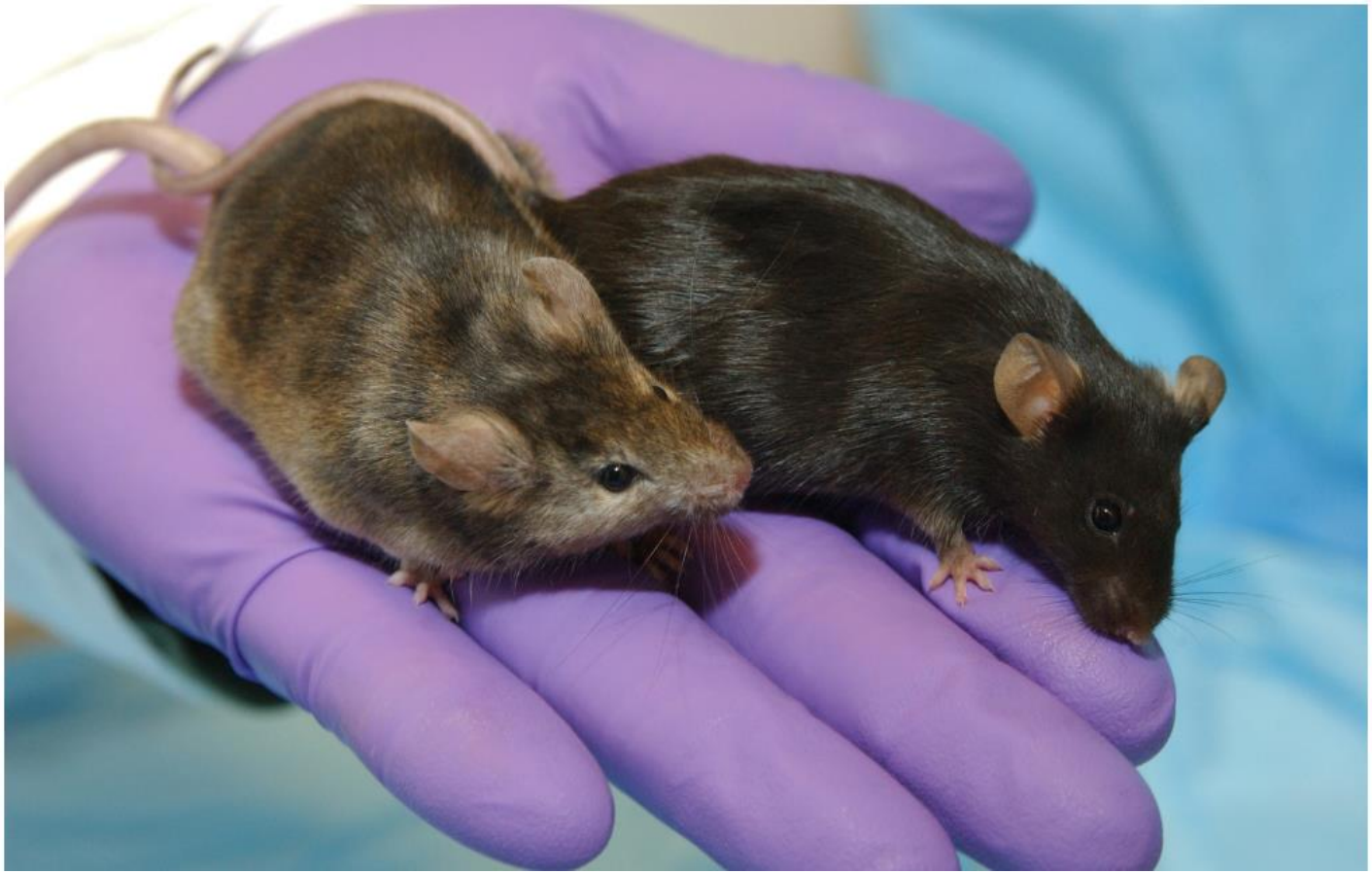
JUNE 21, 2016

New Results From A Rigorous Life Extending Drug Testing Program



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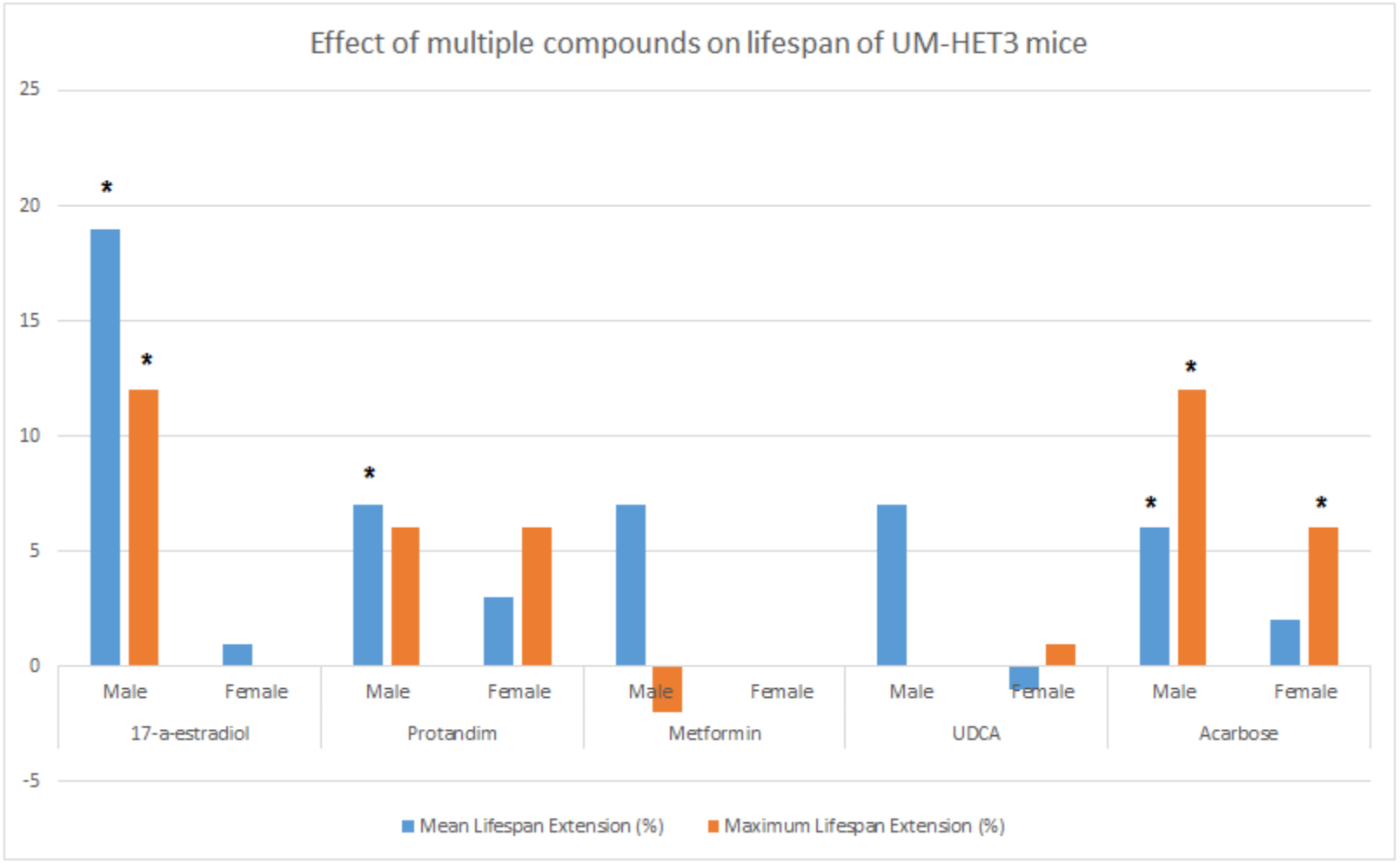

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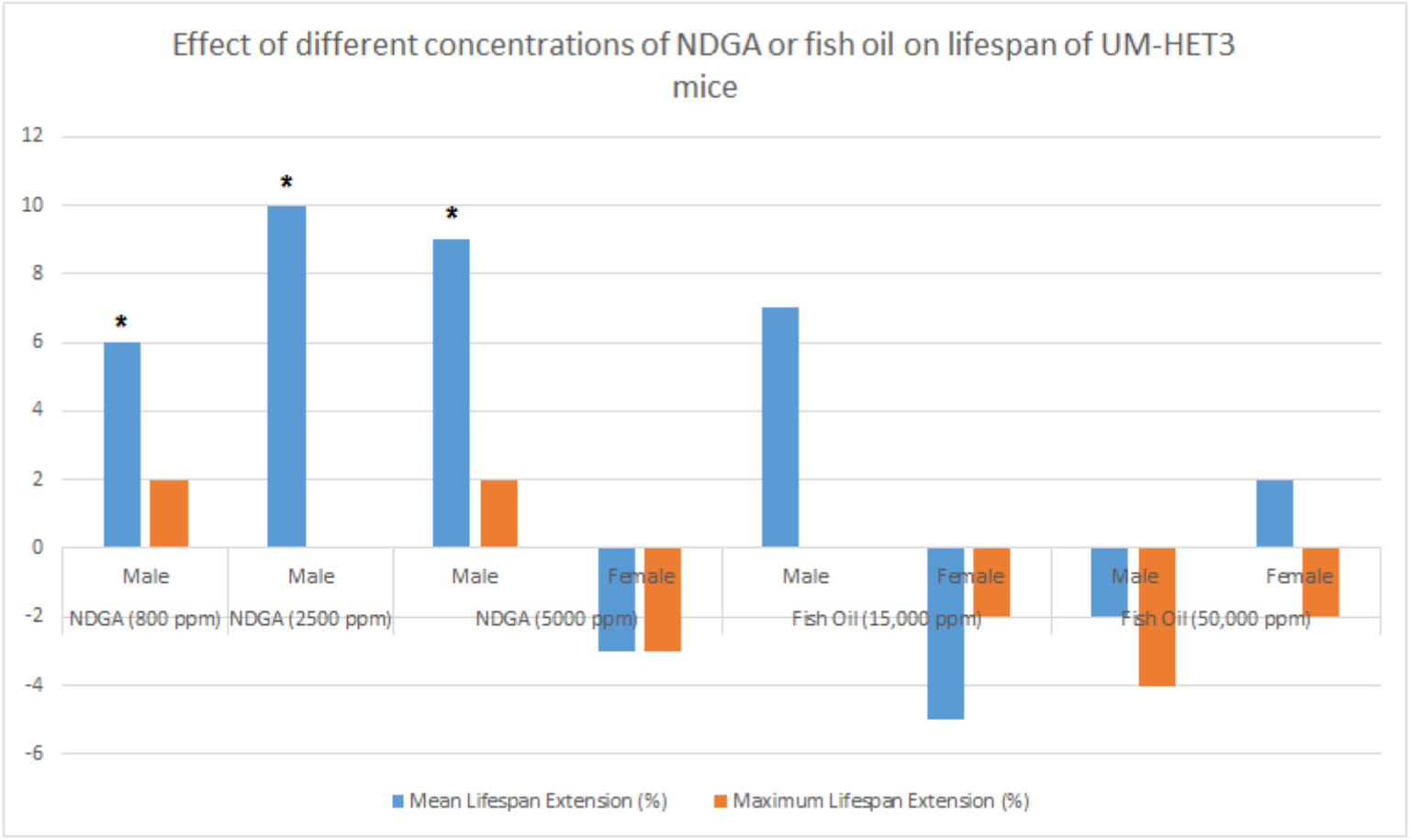

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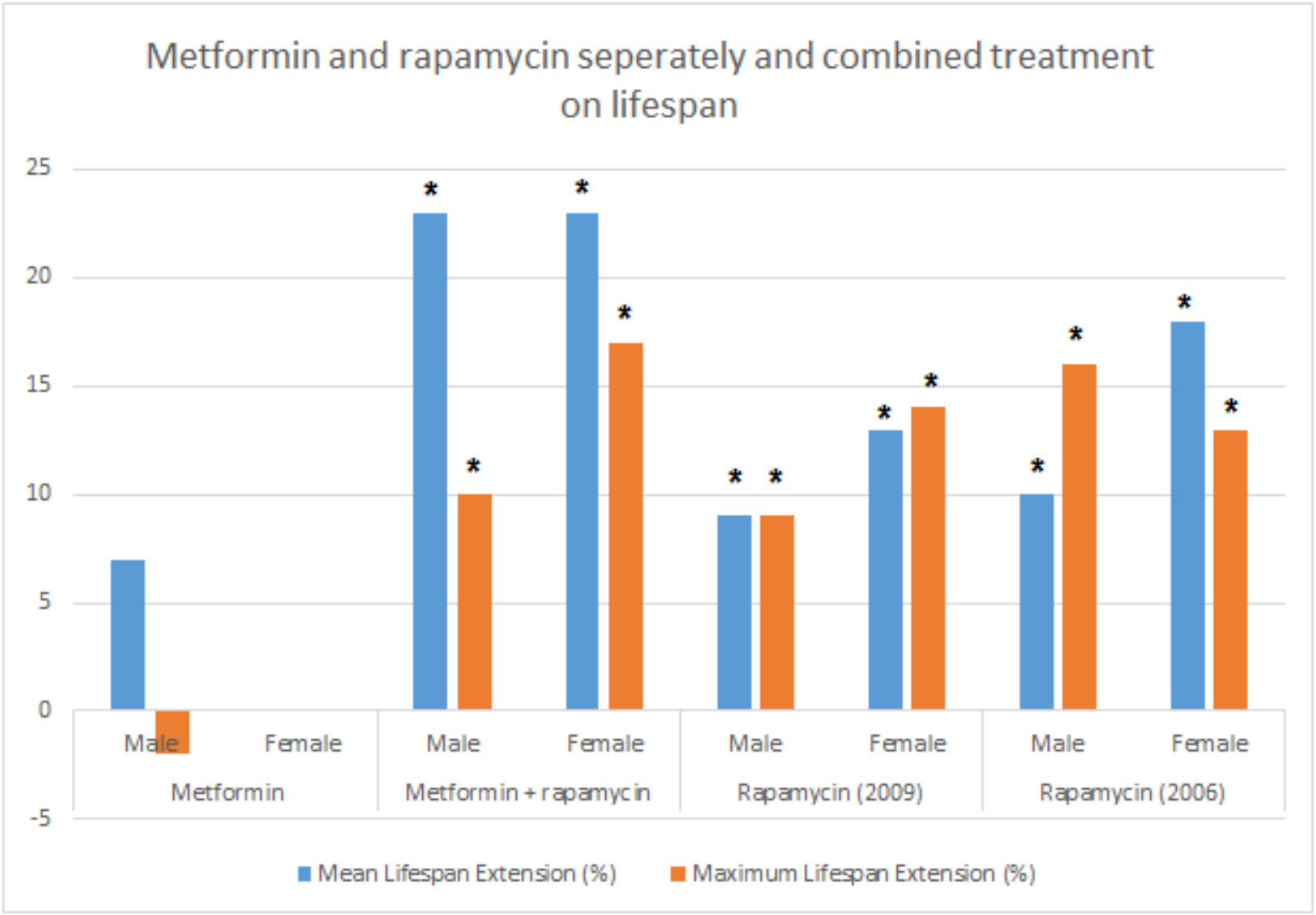

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JUNE 17, 2016

BioViva Seeks To Patent Dual Anti-Aging Gene Therapy

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NAD^+ repletion improves mitochondrial and stem cell function and enhances life span in mice

Abstract

Adult stem cells (SCs) are essential for tissue maintenance and regeneration yet are susceptible to senescence during aging. We demonstrate the importance of the amount of the oxidized form of cellular nicotinamide adenine dinucleotide (NAD^+) and its effect on mitochondrial activity as a pivotal switch to modulate muscle SC (MuSC) senescence. Treatment with the NAD^+ precursor nicotinamide riboside (NR) induced the mitochondrial unfolded protein response and synthesis of prohibitin proteins, and this rejuvenated MuSCs in aged mice. NR also prevented MuSC senescence in the *mdx* (C57BL/10ScSn-*Dmd*^{mdx}/J) mouse model of muscular dystrophy. We furthermore demonstrate that NR delays senescence of neural SCs and melanocyte SCs and increases mouse life span. Strategies that conserve cellular NAD^+ may reprogram dysfunctional SCs and improve life span in mammals.

Tumour resistance in induced pluripotent stem cells derived from naked mole-rats

The naked mole-rat (NMR, *Heterocephalus glaber*), which is the longest-lived rodent species, exhibits extraordinary resistance to cancer. Here we report that NMR somatic cells exhibit a unique tumour-suppressor response to reprogramming induction. In this study, we generate NMR-induced pluripotent stem cells (NMR-iPSCs) and find that NMR-iPSCs do not exhibit teratoma-forming tumorigenicity due to the species-specific activation of tumour-suppressor *alternative reading frame* (*ARF*) and a disruption mutation of the oncogene *ES cell-expressed Ras* (*ERAS*). The forced expression of *Arf* in mouse iPSCs markedly reduces tumorigenicity. Furthermore, we identify an NMR-specific tumour-suppression phenotype—ARF suppression-induced senescence (ASIS)—that may protect iPSCs and somatic cells from ARF suppression and, as a consequence, tumorigenicity. Thus, NMR-specific *ARF* regulation and the disruption of *ERAS* regulate tumour resistance in NMR-iPSCs. Our findings obtained from studies of NMR-iPSCs provide new insight into the mechanisms of tumorigenicity in iPSCs and cancer resistance in the NMR.

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Effects of Sex, Strain, and Energy Intake on Hallmarks of Aging in Mice

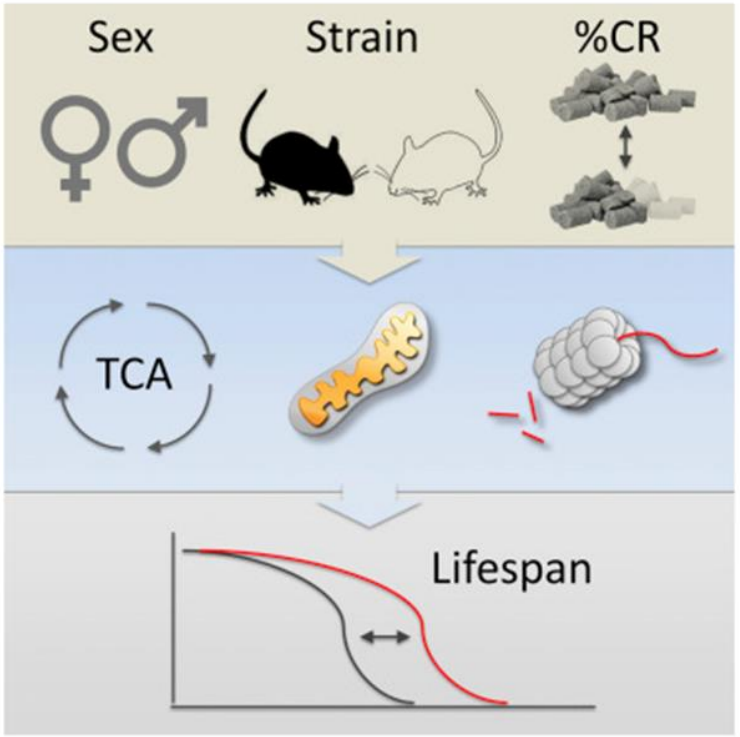
Highlights

- Caloric restriction (CR) prevents the age-related decline in proteostasis
- Mitochondrial function is necessary for lifespan extension through CR
- Health and survival outcomes are separated in response to CR in mice
- The CR response depends on strain, sex, and level of CR

Summary

Calorie restriction (CR) is the most robust non-genetic intervention to delay aging. However, there are a number of emerging experimental variables that alter CR responses. We investigated the role of sex, strain, and level of CR on health and survival in mice. CR did not always correlate with lifespan extension, although it consistently improved health across strains and sexes. Transcriptional and metabolomics changes driven by CR in liver indicated anaplerotic filling of the Krebs cycle together with fatty acid fueling of mitochondria. CR prevented age-associated decline in the liver proteostasis network while increasing mitochondrial number, preserving mitochondrial ultrastructure and function with age. Abrogation of mitochondrial function negated life-prolonging effects of CR in yeast and worms. Our data illustrate the complexity of CR in the context of aging, with a clear separation of outcomes related to health and survival, highlighting complexities of translation of CR into human interventions.

Graphical Abstract



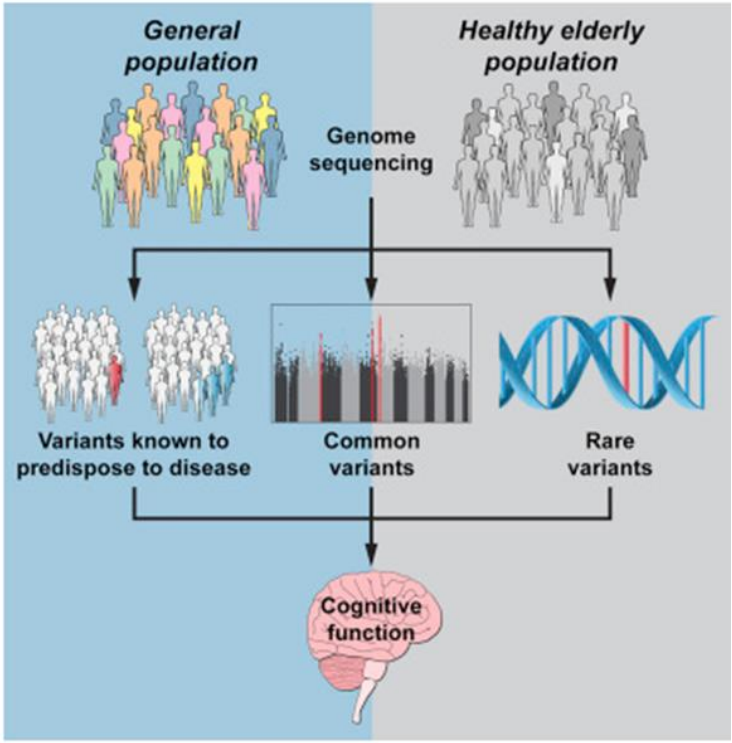
Resource

Whole-Genome Sequencing of a Healthy Aging Cohort

Highlights

- Healthy aging is a complex polygenic trait related but distinct from longevity
- Healthy aging is associated with decreased genetic risk for select diseases
- Healthy aging is potentially linked to protection against cognitive decline
- Genome data are made available for further analysis

Graphical Abstract | Video Abstract



Summary

Studies of long-lived individuals have revealed few genetic mechanisms for protection against age-associated disease. Therefore, we pursued genome sequencing of a related phenotype—healthy aging—to understand the genetics of disease-free aging without medical intervention. In contrast with studies of exceptional longevity, usually focused on centenarians, healthy aging is not associated with known longevity variants, but is associated with reduced genetic susceptibility to Alzheimer and coronary artery disease. Additionally, healthy aging is not associated with a decreased rate of rare pathogenic variants, potentially indicating the presence of disease-resistance factors. In keeping with this possibility, we identify suggestive common and rare variant genetic associations implying that protection against cognitive decline is a genetic component of healthy aging. These findings, based on a relatively small cohort, require independent replication. Overall, our results suggest healthy aging is an overlapping but distinct phenotype from exceptional longevity that may be enriched with disease-protective genetic factors.

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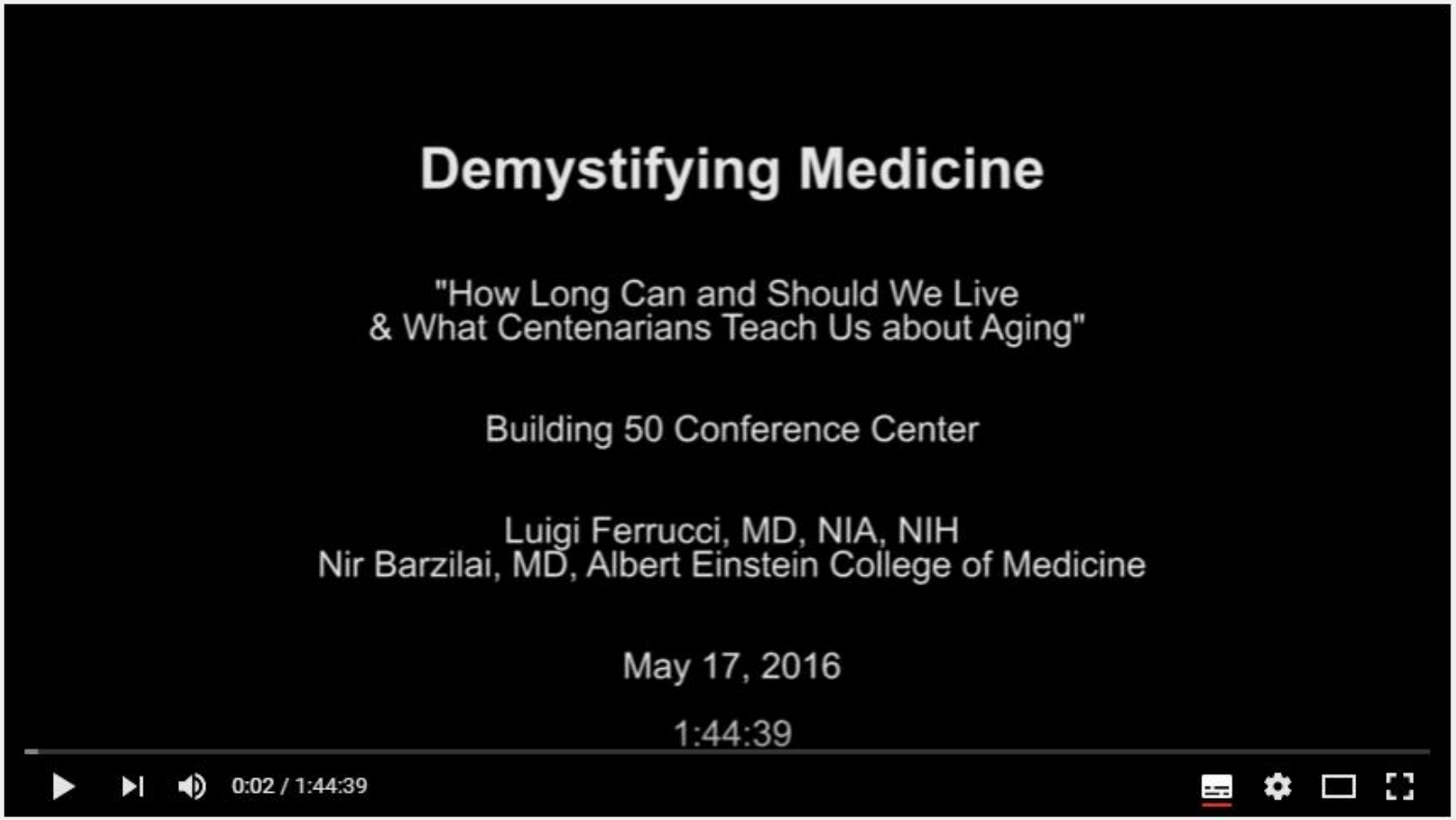
An anticancer drug suppresses the primary nucleation reaction that initiates the production of the toxic Aβ42 aggregates linked with Alzheimer's disease

Abstract

The conversion of the β-amyloid (Aβ) peptide into pathogenic aggregates is linked to the onset and progression of Alzheimer's disease. Although this observation has prompted an extensive search for therapeutic agents to modulate the concentration of Aβ or inhibit its aggregation, all clinical trials with these objectives have so far failed, at least in part because of a lack of understanding of the molecular mechanisms underlying the process of aggregation and its inhibition. To address this problem, we describe a chemical kinetics approach for rational drug discovery, in which the effects of small molecules on the rates of specific microscopic steps in the self-assembly of Aβ42, the most aggregation-prone variant of Aβ, are analyzed quantitatively. By applying this approach, we report that bexarotene, an anticancer drug approved by the U.S. Food and Drug Administration, selectively targets the primary nucleation step in Aβ42 aggregation, delays the formation of toxic species in neuroblastoma cells, and completely suppresses Aβ42 deposition and its consequences in a *Caenorhabditis elegans* model of Aβ42-mediated toxicity. These results suggest that the prevention of the primary nucleation of Aβ42 by compounds such as bexarotene could potentially reduce the risk of onset of Alzheimer's disease and, more generally, that our strategy provides a general framework for the rational identification of a range of candidate drugs directed against neurodegenerative disorders.

REVIEWS/COMMENTS/EDITORIALS



Demystifying Medicine 2016: How Long Can and Should We Live & What Centenarians Teach Us about Aging

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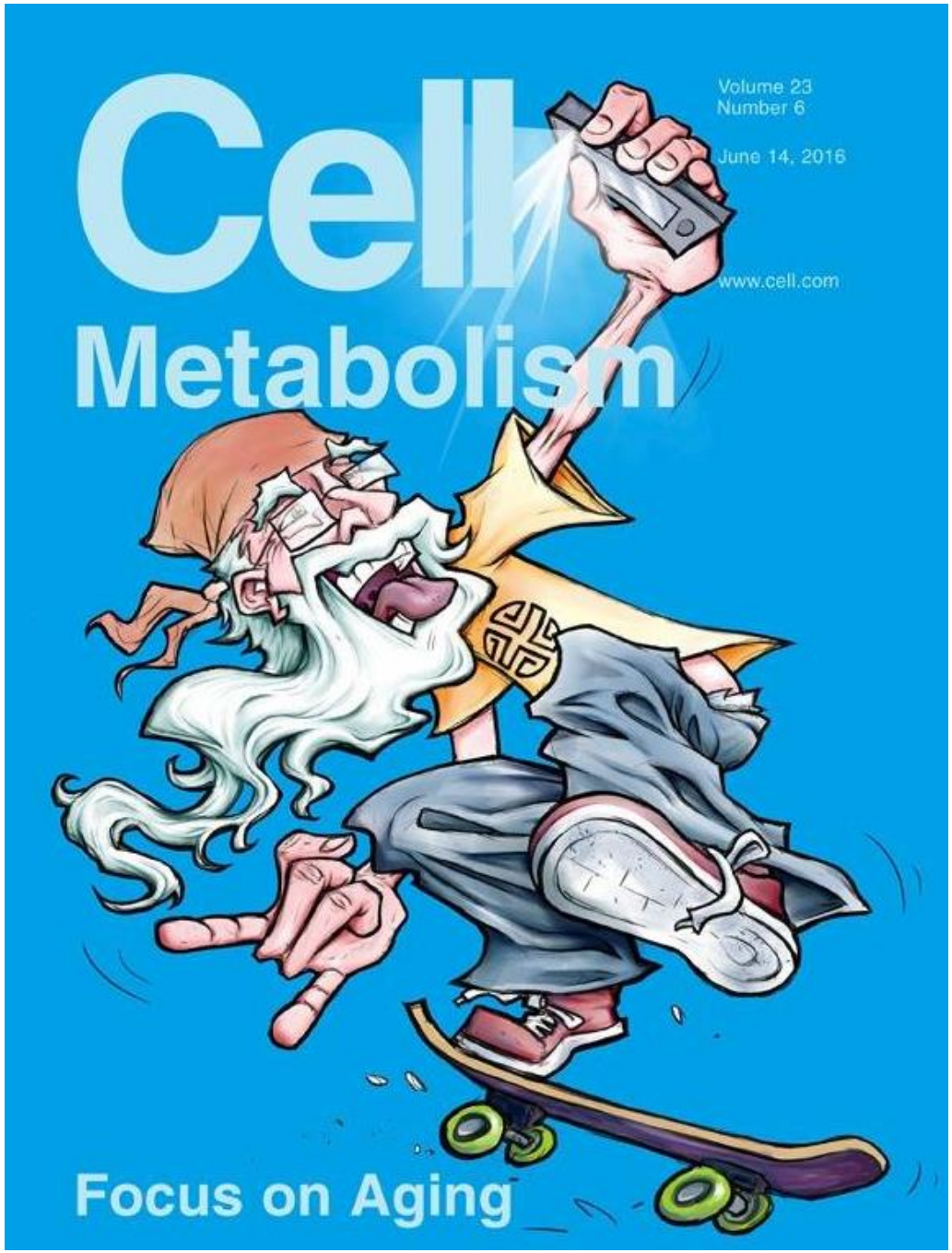

Special Issue

- The Somatotropic Axis in Human Aging: Framework for the Current State of Knowledge and Future Research
  Sofiya Milman, Derek M. Huffman, Nir Barzilai
  In Brief | Full-Text HTML | PDF

- The Mechanistic Target of Rapamycin: The Grand ConducTOR of Metabolism and Aging
  Brian K. Kennedy, Dudley W. Lamming
  In Brief | Full-Text HTML | PDF

- A Ribosomal Perspective on Proteostasis and Aging
  Kristan K. Steffen, Andrew Dillin
  In Brief | Full-Text HTML | PDF

- From Ancient Pathways to Aging Cells—Connecting Metabolism and Cellular Senescence
  Christopher D. Wiley, Judith Campisi
  In Brief | Full-Text HTML | PDF

- Sex Differences in Lifespan
  Steven N. Austad, Kathleen E. Fischer
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- Exercise Promotes Healthy Aging of Skeletal Muscle
  Gregory D. Cartee, Russell T. Hepple, Marcas M. Bamman, Juleen R. Zierath
  In Brief | Full-Text HTML | PDF

- Fasting, Circadian Rhythms, and Time-Restricted Feeding in Healthy Lifespan
  Valter D. Longo, Satchidananda Panda
  In Brief | Full-Text HTML | PDF

- Metformin as a Tool to Target Aging
  Nir Barzilai, Jill P. Crandall, Stephen B. Kritchevsky, Mark A. Espeland
  In Brief | Full-Text HTML | PDF

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AGEING

The yin and yang of mitochondrial dysfunction

Kim Baumann

Nature Reviews Molecular Cell Biology **17**, 331 (2016) | doi:10.1038/nrm.2016.71
Published online 23 May 2016

Mitochondrial dysfunction is a hallmark of organismal ageing, but mild mitochondrial stress during development is also known to have beneficial effects, delaying the ageing process. This positive effect on lifespan has been linked to the activation of the mitochondrial unfolded protein response (UPR^{mt}), which is a stress response that leads to the transcriptional activa…

V. Summersby/NPG

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Stop pulling my strings — what telomeres taught us about the DNA damage response

Mammalian cells have evolved specialized mechanisms to sense and repair double-strand breaks (DSBs) to maintain genomic stability. However, in certain cases, the activity of these pathways can lead to aberrant DNA repair, genomic instability and tumorigenesis. One such case is DNA repair at the natural ends of linear chromosomes, known as telomeres, which can lead to chromosome-end fusions. Here, we review data obtained over the past decade and discuss the mechanisms that protect mammalian chromosome ends from the DNA damage response. We also discuss how telomere research has helped to uncover key steps in DSB repair. Last, we summarize how dysfunctional telomeres and the ensuing genomic instability drive the progression of cancer.

Review

iPSCs: On the Road to Reprogramming Aging

Clara Soria-Valles, Carlos López-Otín

Aging is characterized by irreversible loss of physiological integrity, often accompanied by an organism's loss of function and increased vulnerability to death. Defects in the mechanisms preserving cellular homeostasis over time may give rise to accelerated aging. Somatic cell reprogramming of aged cells can be associated with rejuvenation, erasing certain age-associated features, and illustrating the reversibility potential of aging. Here, we focus on recent advances in the generation of human induced pluripotent stem cells from progeroid syndromes and late-onset diseases such as Alzheimer's or Parkinson's. These cellular models have contributed to a better understanding of such pathologies, as well as to the development of novel therapeutic approaches. We also discuss different strategies to identify and target age-associated reprogramming barriers to facilitate the treatment of age-related disorders.

OTHER RESEARCH

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Federal advisory committee greenlights first CRISPR clinical trial

The technique's first test in people could begin as early as the end of this year.

Sara Reardon

22 June 2016

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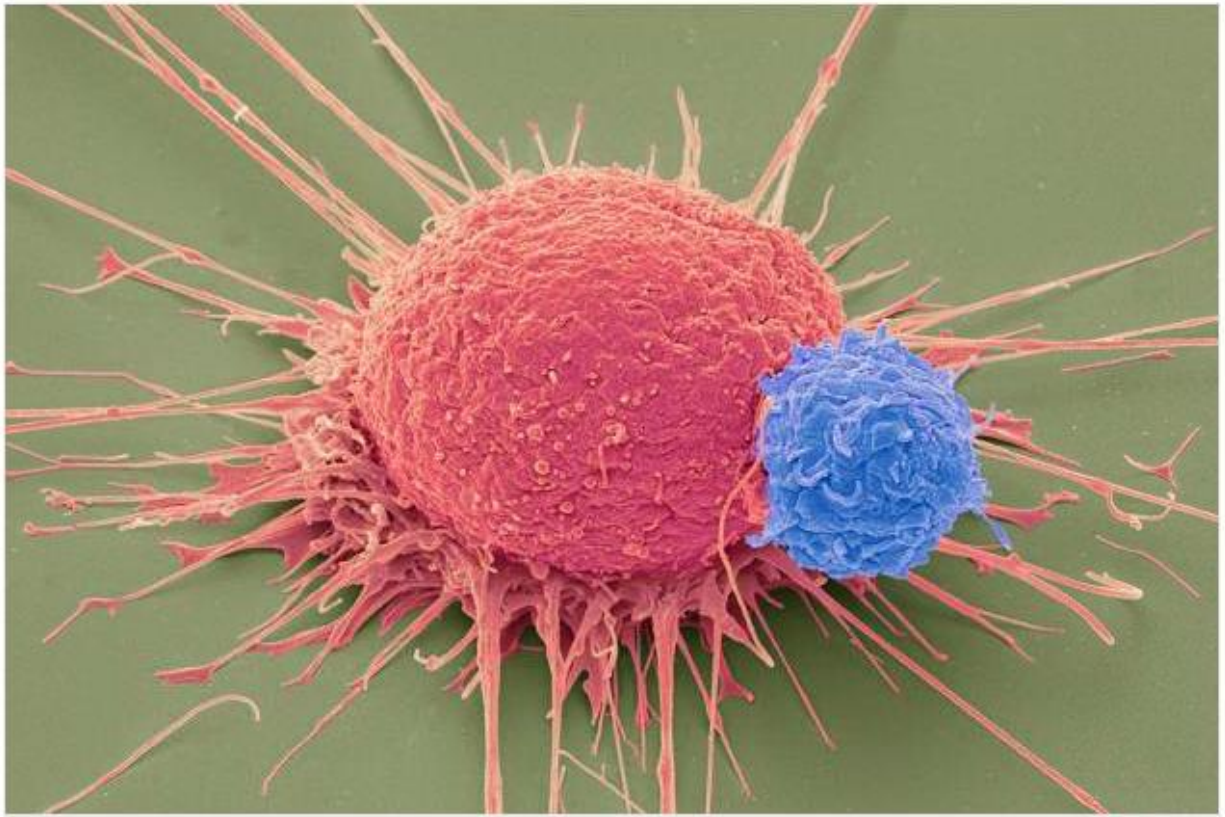

STEVE GSCHMEISSNER/SPL

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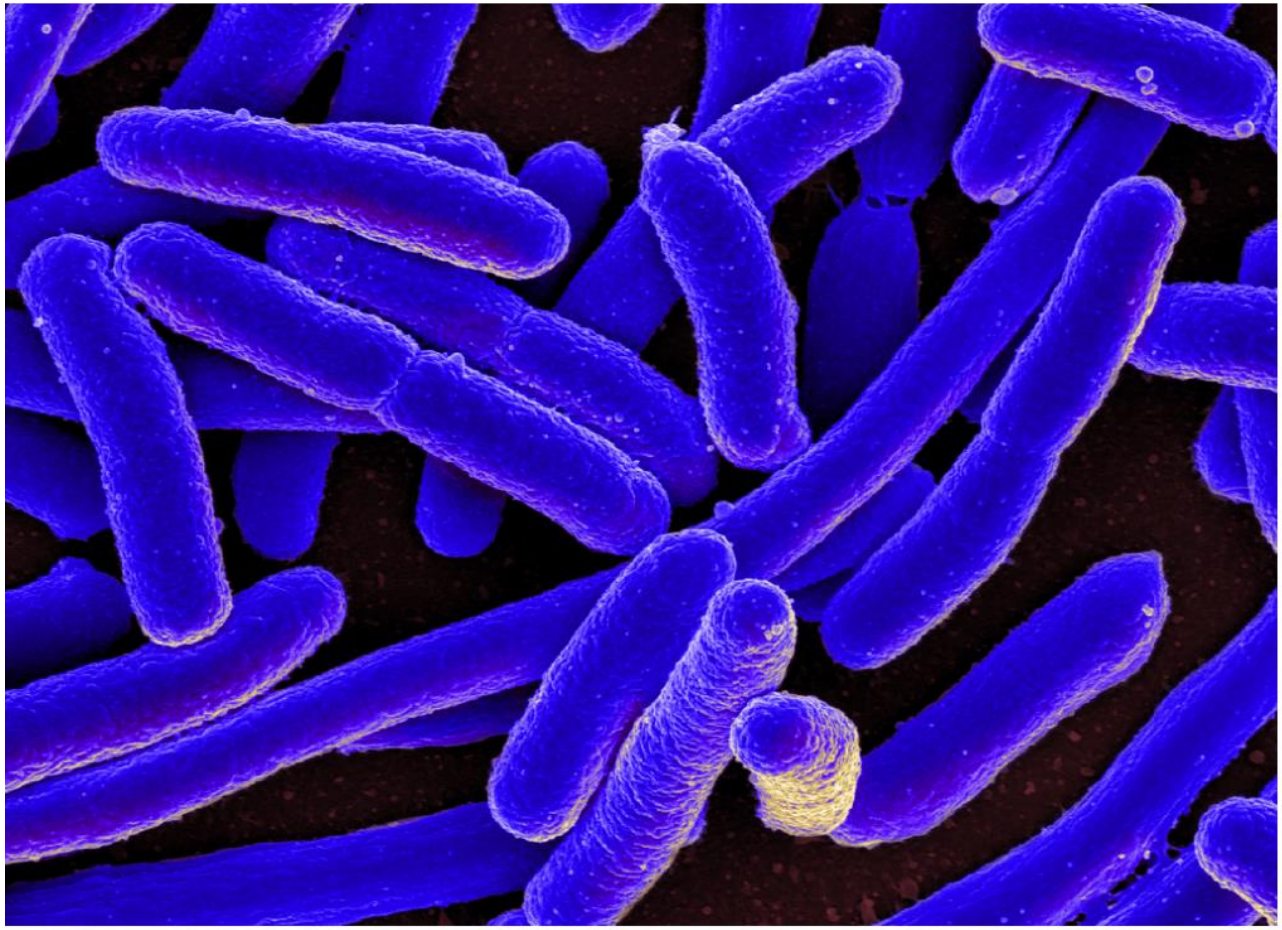
New Insights Into The Gut Microbiome: These Bacteria Influence Your Health More Than You Might Suspect!



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Population-level analysis of gut microbiome variation

Gwen Falony[1,2,*], Marie Joossens[1,2,3,*], Sara Vieira-Silva[1,2,*], Jun Wang[1,2,*], Youssef Darzi[1,2,3], Karoline Faust[1,2,3], Alexander Kurilshikov[4,5], Marc Jan Bonder[6], Mireia Valles-Colomer[1,2], Doris Vandeputte[1,2,3], Raul Y. Tito[1,2,3], Samuel Chaffron[1,2,3], Leen Rymenans[1,2,3], Chloë Verspecht[1,2], Lise De Sutter[1,2,3], Gipsi Lima-Mendez[1,2], Kevin D'hoe[1,2,3], Karl Jonckheere[2,3], Daniel Homola[2,3,†], Roberto Garcia[2,3], Ettje F. Tigchelaar[6,7], Linda Eeckhaudt[2,3], Jingyuan Fu[6,8], Liesbet Henckaerts[1,9], Alexandra Zhernakova[6,7], Cisca Wijmenga[6], Jeroen Raes[1,2,3,‡]

Population-based metagenomics analysis reveals markers for gut microbiome composition and diversity

Alexandra Zhernakova[1,2,*], Alexander Kurilshikov[3,4,†], Marc Jan Bonder[1,†], Ettje F. Tigchelaar[1,2,†], Melanie Schirmer[5,6], Tommi Vatanen[5,7], Zlatan Mujagic[2,8], Arnau Vich Vila[9], Gwen Falony[10,11], Sara Vieira-Silva[10,11], Jun Wang[10,11], Floris Imhann[9], Eelke Brandsma[12], Soesma A. Jankipersadsing[1], Marie Joossens[10,11,13], Maria Carmen Cenit[1,14,15], Patrick Deelen[1,16], Morris A. Swertz[1,16], LifeLines cohort study, Rinse K. Weersma[9], Edith J. M. Feskens[2,17], Mihai G. Netea[18], Dirk Gevers[5,‡], Daisy Jonkers[8], Lude Franke[1], Yurii S. Aulchenko[4,19,20,21], Curtis Huttenhower[5,6], Jeroen Raes[10,11,13], Marten H. Hofker[12], Ramnik J. Xavier[5,22,23,24], Cisca Wijmenga[1,*,§], Jingyuan Fu[1,12,*,§]

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Normalizing the environment recapitulates adult human immune traits in laboratory mice

Our current understanding of immunology was largely defined in laboratory mice, partly because they are inbred and genetically homogeneous, can be genetically manipulated, allow kinetic tissue analyses to be carried out from the onset of disease, and permit the use of tractable disease models. Comparably reductionist experiments are neither technically nor ethically possible in humans. However, there is growing concern that laboratory mice do not reflect relevant aspects of the human immune system, which may account for failures to translate disease treatments from bench to bedside[1, 2, 3, 4, 5, 6, 7, 8]. Laboratory mice live in abnormally hygienic specific pathogen free (SPF) barrier facilities. Here we show that standard laboratory mouse husbandry has profound effects on the immune system and that environmental changes produce mice with immune systems closer to those of adult humans. Laboratory mice—like newborn, but not adult, humans—lack effector-differentiated and mucosally distributed memory T cells. These cell populations were present in free-living barn populations of feral mice and pet store mice with diverse microbial experience, and were induced in laboratory mice after co-housing with pet store mice, suggesting that the environment is involved in the induction of these cells. Altering the living conditions of mice profoundly affected the cellular composition of the innate and adaptive immune systems, resulted in global changes in blood cell gene expression to patterns that more closely reflected the immune signatures of adult humans rather than neonates, altered resistance to infection, and influenced T-cell differentiation in response to a *de novo* viral infection. These data highlight the effects of environment on the basal immune state and response to infection and suggest that restoring physiological microbial exposure in laboratory mice could provide a relevant tool for modelling immunological events in free-living organisms, including humans.

Variation in Microbiome LPS Immunogenicity Contributes to Autoimmunity in Humans

Highlights

- Finnish and Estonian infants have a distinct early gut microbiome compared to Russians
- *B. dorei* and other *Bacteroides* species are highly abundant in Finland and Estonia
- *B. dorei* LPS inhibits the immunostimulatory activity of *E. coli* LPS
- LPS from *B. dorei* does not protect NOD mice from type 1 diabetes

Summary

According to the hygiene hypothesis, the increasing incidence of autoimmune diseases in western countries may be explained by changes in early microbial exposure, leading to altered immune maturation. We followed gut microbiome development from birth until age three in 222 infants in Northern Europe, where early-onset autoimmune diseases are common in Finland and Estonia but are less prevalent in Russia. We found that *Bacteroides* species are lowly abundant in Russians but dominate in Finnish and Estonian infants. Therefore, their lipopolysaccharide (LPS) exposures arose primarily from *Bacteroides* rather than from *Escherichia coli*, which is a potent innate immune activator. We show that *Bacteroides* LPS is structurally distinct from *E. coli* LPS and inhibits innate immune signaling and endotoxin tolerance; furthermore, unlike LPS from *E. coli*, *B. dorei* LPS does not decrease incidence of autoimmune diabetes in non-obese diabetic mice. Early colonization by immunologically silencing microbiota may thus preclude aspects of immune education.

Graphical Abstract