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Baseline tumor growth and immune control in laboratory mice are significantly influenced by subthermoneutral housing temperature

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We show here that fundamental aspects of antitumor immunity in mice are significantly influenced by ambient housing temperature. Standard housing temperature for laboratory mice in research facilities is mandated to be between 20–26 °C; however, these subthermoneutral temperatures cause mild chronic cold stress, activating thermogenesis to maintain normal body temperature. When stress is alleviated by housing at thermoneutral ambient temperature (30–31 °C), we observe a striking reduction in tumor formation, growth rate and metastasis. This improved control of tumor growth is dependent upon the adaptive immune system. We observe significantly increased numbers of antigen-specific $CD8^+$ T lymphocytes and $CD8^+$ T cells with an activated phenotype in the tumor microenvironment at thermoneutrality. At the same time there is a significant reduction in numbers of immunosuppressive MDSCs and regulatory T lymphocytes. Notably, in temperature preference studies, tumor-bearing mice select a higher ambient temperature than non-tumor-bearing mice, suggesting that tumor-bearing mice experience a greater degree of cold-stress. Overall, our data raise the hypothesis that suppression of antitumor immunity is an outcome of cold stress-induced thermogenesis. Therefore, the common approach of studying immunity against tumors in mice housed only at standard room temperature may be limiting our understanding of the full potential of the antitumor immune response.

For research facilities, the room temperature that the National Research Council *Guide for the Care and Use of Laboratory Animals* (9) requires is considerably cooler than thermoneutrality to facilitate some aspects of husbandry, to reduce frequency of cage cleaning, and to ensure thermal comfort of animal care technicians (4, 7). Institutes must select and maintain a constant room temperature between 20 °C and 26 °C; until 2011, an even cooler range between 18 °C and 24 °C was permitted. Despite the significant impact of ambient temperature on the metabolism of laboratory mice, the room temperature of mouse colonies has not concerned researchers because mice are able to maintain a normal body temperature. However, cool housing temperature is not always a benign variable and there is a disconcerting possibility that it may affect the outcome of a broad range of experimental endpoints (4, 5, 7). Although researchers interested in measuring fever in LPS-treated rodents have long recognized the importance of ambient temperature (4, 10), more recent studies demonstrate that an expected obesity phenotype in uncoupling protein 1 (UCP1)-deficient mice could only be observed when mice were housed at thermoneutrality (11). In another study, it was shown that adaptation to standard

Significance

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PLOS ONE

Evolution of Human Longevity Uncoupled from Caloric Restriction Mechanisms

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Abstract

Caloric restriction (CR) and chemical agents, such as resveratrol and rapamycin that partially mimic the CR effect, can delay morbidity and mortality across a broad range of species. In humans, however, the effects of CR or other life-extending agents have not yet been investigated systematically. Human maximal lifespan is already substantially greater compared to that of closely related primate species. It is therefore possible that humans have acquired genetic mutations that mimic the CR effect. Here, we tested this notion by comparing transcriptome differences between humans and other primates, with the transcriptome changes observed in mice subjected to CR. We show that the human transcriptome state, relative to other primate transcriptomes, does not match that of the CR mice or mice treated with resveratrol, but resembles the transcriptome state of *ad libitum* fed mice. At the same time, the transcriptome changes induced by CR in mice are enriched among genes showing age-related changes in primates, concentrated in specific expression patterns, and can be linked with specific functional pathways, including insulin signalling, cancer, and the immune response. These findings indicate that the evolution of human longevity was likely independent of CR-induced lifespan extension mechanisms. Consequently, application of CR or CR-mimicking agents may yet offer a promising direction for the extension of healthy human lifespan.

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Mice Fed Rapamycin Have an Increase in Lifespan Associated with Major Changes in the Liver Transcriptome

Abstract

Rapamycin was found to increase (11% to 16%) the lifespan of male and female C57BL/6J mice most likely by reducing the increase in the hazard for mortality (i.e., the rate of aging) term in the Gompertz mortality analysis. To identify the pathways that could be responsible for rapamycin's longevity effect, we analyzed the transcriptome of liver from 25-month-old male and female mice fed rapamycin starting at 4 months of age. Few changes (<300 transcripts) were observed in transcriptome of rapamycin-fed males; however, a large number of transcripts (>4,500) changed significantly in females. Using multidimensional scaling and heatmap analyses, the male mice fed rapamycin were found to segregate into two groups: one group that is almost identical to control males (Rapa-1) and a second group (Rapa-2) that shows a change in gene expression (>4,000 transcripts) with more than 60% of the genes shared with female mice fed Rapa. Using ingenuity pathway analysis, 13 pathways were significantly altered in both Rapa-2 males and rapamycin-fed females with mitochondrial function as the most significantly changed pathway. Our findings show that rapamycin has a major effect on the transcriptome and point to several pathways that would likely impact the longevity.

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ARTICLE

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Stimulus-triggered fate conversion of somatic cells into pluripotency

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Here we report a unique cellular reprogramming phenomenon, called stimulus-triggered acquisition of pluripotency (STAP), which requires neither nuclear transfer nor the introduction of transcription factors. In STAP, strong external stimuli such as a transient low-pH stressor reprogrammed mammalian somatic cells, resulting in the generation of pluripotent cells. Through real-time imaging of STAP cells derived from purified lymphocytes, as well as gene rearrangement analysis, we found that committed somatic cells give rise to STAP cells by reprogramming rather than selection. STAP cells showed a substantial decrease in DNA methylation in the regulatory regions of pluripotency marker genes. Blastocyst injection showed that STAP cells efficiently contribute to chimaeric embryos and to offspring via germline transmission. We also demonstrate the derivation of robustly expandable pluripotent cell lines from STAP cells. Thus, our findings indicate that epigenetic fate determination of mammalian cells can be markedly converted in a context-dependent manner by strong environmental cues.

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LETTER

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Bidirectional developmental potential in reprogrammed cells with acquired pluripotency

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We recently discovered an unexpected phenomenon of somatic cell reprogramming into pluripotent cells by exposure to sublethal stimuli, which we call stimulus-triggered acquisition of pluripotency (STAP)[1]. This reprogramming does not require nuclear transfer[2,3] or genetic manipulation[4]. Here we report that reprogrammed STAP cells, unlike embryonic stem (ES) cells, can contribute to both embryonic and placental tissues, as seen in a blastocyst injection assay. Mouse STAP cells lose the ability to contribute to the placenta as well as trophoblast marker expression on converting into ES-like stem cells by treatment with adrenocorticotropic hormone (ACTH) and leukaemia inhibitory factor (LIF). In contrast, when cultured with Fgf4, STAP cells give rise to proliferative stem cells with enhanced trophoblastic characteristics. Notably, unlike conventional trophoblast stem cells, the Fgf4-induced stem cells from STAP cells contribute to both embryonic and placental tissues *in vivo* and transform into ES-like cells when cultured with LIF-containing medium. Taken together, the developmental potential of STAP cells, shown by chimaera formation and *in vitro* cell conversion, indicates that they represent a unique state of pluripotency.

We recently discovered an intriguing phenomenon of cellular fate conversion: somatic cells regain pluripotency after experiencing sublethal stimuli such as a low-pH exposure[1]. When splenic $CD45^+$ lymphocytes are exposed to pH 5.7 for 30 min and subsequently cultured in the presence of LIF, a substantial portion of surviving cells start to express the pluripotent cell marker Oct4 (also called Pou5f1) at day 2. By day 7, pluripotent cell clusters form with a bona fide pluripotency marker profile and acquire the competence for three-germ-layer differentiation as shown by teratoma formation. These STAP cells can also efficiently contribute to chimaeric mice and undergo germline transmission using a blastocyst injection assay[1]. Although these characteristics resemble those of ES cells, STAP cells seem to differ from ES cells in their limited capacity for self-renewal (typically, for only a few

Primate energy expenditure and life history

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Humans and other primates are distinct among placental mammals in having exceptionally slow rates of growth, reproduction, and aging. Primates' slow life history schedules are generally thought to reflect an evolved strategy of allocating energy away from growth and reproduction and toward somatic investment, particularly to the development and maintenance of large brains. Here we examine an alternative explanation: that primates' slow life histories reflect low total energy expenditure (TEE) (kilocalories per day) relative to other placental mammals. We compared doubly labeled water measurements of TEE among 17 primate species with similar measures for other placental mammals. We found that primates use remarkably little energy each day, expending on average only 50% of the energy expected for a placental mammal of similar mass. Such large differences in TEE are not easily explained by differences in physical activity, and instead appear to reflect systemic metabolic adaptation for low energy expenditures in primates. Indeed, comparisons of wild and captive primate populations indicate similar levels of energy expenditure. Broad interspecific comparisons of growth, reproduction, and maximum life span indicate that primates' slow metabolic rates contribute to their characteristically slow life histories.

relationship between BMR and TEE is quite variable, with the ratio of TEE:BMR ranging from less than two to more than seven among mammals (13).

In this study, we examined TEE among primates and other placental mammals to test the hypothesis that evolved differences in the size of the energy budget contribute to the exceptionally slow life histories of primates. Primates are important points of comparison in life history analyses because they have the longest lifespans and the slowest rates of growth and reproduction of any eutherian Order (1, 2). Previous analyses have shown that haplorhine primates (apes, monkeys, and tarsiers) have BMRs similar to other placental mammals, whereas strepsirrhine primates (lemurs and lorisiform primates) have BMRs that are marginally lower (14). BMR does not explain primates' low rates of growth or senescence (7–9), and the slow life histories of primates, particularly of humans and other apes, are instead thought to reflect an evolved reduction in energy allocation to growth and reproduction among primates (1, 2). Before this study there were insufficient data on primate TEE to test an alternative hypothesis: that slow life histories among primates reflect smaller energy budgets

REVIEWS

Extracellular α-synuclein—a novel and crucial factor in Lewy body diseases

He-Jin Lee, Eun-Jin Bae and Seung-Jae Lee

Abstract | Misfolding and intracellular aggregation of α-synuclein are thought to be crucial factors in the pathogenesis of Lewy body diseases (LBDs), such as Parkinson disease. However, the pathogenic modifications of this protein and the mechanisms underlying its activity have not been fully characterized. Recent studies suggest that small amounts of α-synuclein are released from neuronal cells by unconventional exocytosis, and that this extracellular α-synuclein contributes to the major pathological features of LBD, such as neurodegeneration, progressive spreading of α-synuclein pathology, and neuroinflammation. In this article, we review a rapidly growing body of literature on possible mechanisms by which extracellular α-synuclein contributes to LBD pathology, and discuss therapeutic approaches to target this form of α-synuclein to halt disease progression.

Lee, H.-J. *et al. Nat. Rev. Neurol.* advance online publication 28 January 2014; doi:10.1038/nrneurol.2013.275

REVIEWS

Risk estimation in rheumatoid arthritis —from bench to bedside

Annette H. M. van der Helm-van Mil

Abstract | The prognosis for patients with rheumatoid arthritis (RA) who were diagnosed in the years since 2010 is much better than for individuals who were diagnosed with the disease 20 years ago. This improvement in the long-term outcome of disease is the result of earlier initiation of therapy, disease-activity-guided modification of treatment and the availability of new, and effective, drugs. Nonetheless, current treatment strategies remain population-based, rather than individualized. Decision-making processes relevant to the provision of individualized treatment require appropriate prognostication with regard to a number of variables. Here, the methods available to evaluate the performance of predictive models are discussed. In addition, I highlight the advances in risk estimation that have been made concerning three treatment decisions relevant to the management of RA that are made daily in the clinic: when to initiate treatment with DMARDs in patients in the early stages of arthritis; the ideal intensity of initial treatment; and the likely responsiveness of the patient to a particular therapy. Apart from a model predicting the development of RA, the majority of prognostic tools derived in arthritis and RA are not accurate or not validated. Hence, personalized treatment decisions in arthritis and RA are still far from bedside.

van der Helm-van Mil, A. H. M. *Nat. Rev. Rheumatol.* advance online publication 28 January 2014; doi:10.1038/nrrheum.2013.215

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Progeria: A Paradigm for Translational Medicine

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Rare diseases are powerful windows into biological processes and can serve as models for the development of therapeutic strategies. The progress made on the premature aging disorder Progeria is a shining example of the impact that studies of rare diseases can have.

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Pluripotent stem cells in regenerative medicine: challenges and recent progress

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Abstract | After years of incremental progress, several recent studies have succeeded in deriving disease-relevant cell types from human pluripotent stem cell (hPSC) sources. The prospect of an unlimited cell source, combined with promising preclinical data, indicates that hPSC technology may be on the verge of clinical translation. In this Review, we discuss recent progress in directed differentiation, some of the new technologies that have facilitated the success of hPSC therapies and the remaining hurdles on the road towards developing hPSC-based cell therapies.