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Naked mole-rat has increased translational fidelity compared with the mouse, as well as a unique 28S ribosomal RNA cleavage

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The naked mole-rat (*Heterocephalus glaber*) is a subterranean eusocial rodent with a markedly long lifespan and resistance to tumorigenesis. Multiple data implicate modulation of protein translation in longevity. Here we report that 28S ribosomal RNA (rRNA) of the naked mole-rat is processed into two smaller fragments of unequal size. The two breakpoints are located in the 28S rRNA divergent region 6 and excise a fragment of 263 nt. The excised fragment is unique to the naked mole-rat rRNA and does not show homology to other genomic regions. Because this hidden break site could alter ribosome structure, we investigated whether translation rate and amino acid incorporation fidelity were altered. We report that naked mole-rat fibroblasts have significantly increased translational fidelity despite having comparable translation rates with mouse fibroblasts. Although we cannot directly test whether the unique 28S rRNA structure contributes to the increased fidelity of translation, we speculate that it may change the folding or dynamics of the large ribosomal subunit, altering the rate of GTP hydrolysis and/or interaction of the large subunit with tRNA during accommodation, thus affecting the fidelity of protein synthesis. In summary, our results show that naked mole-rat cells produce fewer aberrant proteins, supporting the hypothesis that the more stable proteome of the naked mole-rat contributes to its longevity.

aging | NMR

pathway is the promotion of protein translation in response to nutrients. Modulating the mTOR pathway genetically or pharmacologically, using the inhibitor rapamycin, has been shown to extend lifespan in yeast, *Caenorhabditis elegans*, *Drosophila*, and mice (14). The exact mechanism by which modulating protein translation via inhibition of mTOR extends lifespan is unclear. Two major explanations that were proposed are global reduction in mRNA translation, leading to better maintenance of protein homeostasis, or differential translation of specific mRNAs beneficial for longevity and stress resistance (reviewed in ref. 13).

Proper protein folding and stability are heavily implicated in aging. Overexpression of heat shock transcription factors and chaperones that aid protein folding can extend lifespan in *Drosophila melanogaster* (16) and *C. elegans* (17, 18). In bacteria, aging occurs by asymmetrical segregation of protein aggregates (19), and a similar mechanism has been described in yeast (20). The formation of aggregates as a result of mistranslated polypeptides has been implicated in several aging-related diseases such as amyotrophic lateral sclerosis, Huntington's disease, and Alzheimer's disease (21). A major factor determining proteome quality is translational fidelity of the ribosome. Severe disruptions of translational fidelity have been shown to cause accumulation of aggregates and pathological neurodegeneration (22).

The connection between translation and aging led us to examine NMR ribosomes for longevity-promoting phenotypes such

Sirt1 Extends Life Span and Delays Aging in Mice through the Regulation of Nk2 Homeobox 1 in the DMH and LH

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SUMMARY

The mammalian Sir2 ortholog Sirt1 plays an important role in metabolic regulation. However, the role of Sirt1 in the regulation of aging and longevity is still controversial. Here we demonstrate that brain-specific *Sirt1*-overexpressing (BRASTO) transgenic mice show significant life span extension in both males and females, and aged BRASTO mice exhibit phenotypes consistent with a delay in aging. These phenotypes are mediated by enhanced neural activity specifically in the dorsomedial and lateral hypothalamic nuclei (DMH and LH, respectively), through increased orexin type 2 receptor (*Ox2r*) expression. We identified Nk2 homeobox 1 (*Nkx2-1*) as a partner of Sirt1 that upregulates *Ox2r* transcription and colocalizes with Sirt1 in the DMH and LH. DMH/LH-specific knockdown of *Sirt1*, *Nkx2-1*, or *Ox2r* and DMH-specific *Sirt1* overexpression further support the role of Sirt1/*Nkx2-1*/*Ox2r*-mediated signaling for longevity-associated phenotypes. Our findings indicate the importance of DMH/LH-predominant Sirt1 activity in the regulation of aging and longevity in mammals.

in worms and flies have also suggested that systemic interplay between multiple tissues regulates aging and longevity (Damonis and Parfimon, 2010; Durieux et al., 2011). In mammals, however, the complexity of tissue interplay is multiplied, and a blueprint for a systemic network regulating aging and longevity still remains elusive. Most recently, it has been shown that hypothalamic NF- κ B signaling plays a critical role in the regulation of systemic aging via immune-neuroendocrine integration in mice, implicating the importance of the hypothalamus in systemic aging/longevity control in mammals (Zhang et al., 2013). Indeed, the hypothalamus communicates with multiple peripheral tissues via hormonal and neural networks and coordinates metabolic and behavioral responses to nutritional and environmental stimuli. For instance, neurons producing growth hormone (GH)-releasing hormone and somatostatin that stimulate and inhibit GH release in the anterior pituitary gland, respectively, are localized in the hypothalamus. The growth hormone (GH)/IGF-1 axis, which regulates somatic growth, metabolism, and tissue repair, has been well established to control aging and longevity in mammals (Bartke, 2011). Therefore, this particular tissue in the brain appears to function as a critical juncture for the coordination of metabolic signaling and aging/longevity control in mammals.

Sir2 (silent information regulator 2) family proteins, now called "sirtuins," have been demonstrated to coordinate metabolic responses to changes in nutritional availability and maintain physiological homeostasis in mammals (Haigis and Sinclair, 2010). These functions of sirtuins are ascribed to their unique NAD-

PDK1 decreases TACE-mediated α -secretase activity and promotes disease progression in prion and Alzheimer's diseases

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α -secretase-mediated cleavage of amyloid precursor protein (APP) precludes formation of neurotoxic amyloid- β (A β) peptides, and α -cleavage of cellular prion protein (PrP^C) prevents its conversion into misfolded, pathogenic prions (PrP^{Sc}). The mechanisms leading to decreased α -secretase activity in Alzheimer's and prion disease remain unclear. Here, we find that tumor necrosis factor- α -converting enzyme (TACE)-mediated α -secretase activity is impaired at the surface of neurons infected with PrP^{Sc} or isolated from APP-transgenic mice with amyloid pathology. 3-phosphoinositide-dependent kinase-1 (PDK1) activity is increased in neurons infected with prions or affected by A β deposition and in the brains of individuals with Alzheimer's disease. PDK1 induces phosphorylation and caveolin-1-mediated internalization of TACE. This dysregulation of TACE increases PrP^{Sc} and A β accumulation and reduces shedding of TNF- α receptor type 1 (TNFR1). Inhibition of PDK1 promotes localization of TACE to the plasma membrane, restores TACE-dependent α -secretase activity and cleavage of APP, PrP^C and TNFR1, and attenuates PrP^{Sc}- and A β -induced neurotoxicity. In mice, inhibition or siRNA-mediated silencing of PDK1 extends survival and reduces motor impairment following PrP^{Sc} infection and in APP-transgenic mice reduces Alzheimer's disease-like pathology and memory impairment.

ORIGINAL RESEARCH COMMUNICATION

Aspirin Inhibits Oxidant Stress, Reduces Age-Associated Functional Declines, and Extends Lifespan of *Caenorhabditis elegans*

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Abstract

Aims: Oxidative stress and inflammation are leading risk factors for age-associated functional declines. We assessed aspirin effects on endogenous oxidative-stress levels, lifespan, and age-related functional declines, in the nematode *Caenorhabditis elegans*. **Results:** Both aspirin and its salicylate moiety, at nontoxic concentrations (0.5–1 mM), attenuated endogenous levels of reactive oxygen species ($p < 0.001$), and upregulated antioxidant genes encoding superoxide dismutases (especially *sod-3*, $p < 0.001$), catalases (especially *ctl-2*, $p < 0.0001$), and two glutathione-S-transferases (*gst-4* and *gst-10*; each $p < 0.005$). Aspirin, and to a lesser degree salicylate, improved survival of hydrogen peroxide, and in the absence of exogenous stress aspirin extended lifespan by 21%–23% (each $p < 10^{-9}$), while salicylate added 14% ($p < 10^{-6}$). Aspirin and salicylate delayed age-dependent declines in motility and pharyngeal pumping (each $p < 0.005$), and decreased intracellular protein aggregation ($p < 0.0001$)—all established markers of physiological aging—consistent with slowing of the aging process. Aspirin fails to improve stress resistance or lifespan in nematodes lacking DAF-16, implying that it acts through this FOXO transcription factor. **Innovation:** Studies in mice and humans suggest that aspirin may protect against multiple age-associated diseases by reducing all-cause mortality. We now demonstrate that aspirin markedly slows many measures of aging in the nematode. **Conclusions:** Aspirin treatment is associated with diminished endogenous oxidant stress and enhanced resistance to exogenous peroxide, both likely mediated by activation of antioxidant defenses. Our evidence indicates that aspirin attenuates insulin-like signaling, thus protecting against oxidative stress, postponing age-associated functional declines and extending *C. elegans* lifespan under benign conditions. *Antioxid. Redox Signal.* 18, 481–490.

Low Vitamin D Status Is an Independent Predictor of Increased Frailty and All-Cause Mortality in Older Men: The Health in Men Study

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Context and Objective: Hypovitaminosis D and frailty are common in the older population. We aimed to determine whether 25-hydroxyvitamin D [25(OH)D] concentrations are associated with frailty and mortality.

Design: We conducted a prospective cohort study.

Setting and Participants: Participants included 4203 older men aged 70–88 years in Perth, Western Australia.

Main Outcome Measures: 25(OH)D was measured by immunoassay. Frailty was assessed with the 5-point FRAIL (fatigue, resistance, ambulation, illness, and loss of weight) scale. Mortality was determined from the death registry via the Western Australian Data Linkage System.

Results: At baseline, 676 (16.1%) men were frail, as defined by having ≥ 3 deficits (FRAIL scale ≥ 3). In multivariate cross-sectional analysis, low vitamin D status, defined by the lowest quartile of 25(OH)D values (< 52.9 nmol/L), was associated with increased prevalent frailty (odds ratio, 1.96; 95% confidence interval [CI], 1.52 to 2.52) in comparison to the highest quartile of 25(OH)D values (> 81.6 nmol/L). After a mean period of 5.3 years, the adjusted odds ratio of being frail at follow-up for men with low vitamin D and having zero deficit at baseline (FRAIL scale = 0) was 1.56 (95% CI, 1.07 to 2.27). Low vitamin D also predicted all-cause mortality over a period of up to 9.2 years (hazard ratio, 1.20; 95% CI, 1.02 to 1.42), independent of baseline frailty and other covariates.

Conclusion: Hypovitaminosis D is associated with prevalent and incident frailty in older men. Hypovitaminosis D also predicts all-cause mortality, independent of frailty. The association between vitamin D and mortality is not solely dependent on the occurrence of frailty. (*J Clin Endocrinol Metab* 98: 3821–3828, 2013)

Vitamin D Status Is Associated With Functional Limitations and Functional Decline in Older Individuals

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Context: Vitamin D is known to influence muscle health. A reduction in muscle mass increases the risk of functional limitations among older individuals.

Objective: The aim of this study was to examine the relationship between vitamin D status and functional limitations.

Design, Setting, and Participants: Two independent cohorts of the Longitudinal Aging Study Amsterdam were used. Participants were aged 65 to 88 years (older cohort, $n = 1237$; baseline 1995) and 55 to 65 years (younger cohort, $n = 725$; baseline 2002).

Main Outcome Measures: Questions on the ability and degree of difficulty to perform 6 functions of daily life were asked.

Results: Of the participants, 56% in the older cohort and 30% in the younger cohort had ≥ 1 limitation. Vitamin D deficiency (25-hydroxyvitamin D level of <20 ng/mL) compared with the value in the reference group (>30 ng/mL) was related to the presence of functional limitations at baseline (odds ratio [OR] = 1.7; 95% confidence interval [CI], 1.2–2.5 and OR = 2.2; 95% CI 1.3–3.7 for the older and younger cohorts, respectively). In the older cohort, vitamin D deficiency was associated with an increase in limitations at 3 years (OR = 2.0; 95% CI, 1.1–3.5), whereas vitamin D deficiency in the younger cohort was associated with an increase in limitations at 6 years (OR = 3.3; 95% CI, 1.1–10.1). Analyses were adjusted for confounders.

Conclusion: Vitamin D status is associated with functional limitations cross-sectionally and longitudinally in individuals aged 55 to 65 years and those 65 years and older. The possible association of vitamin D with functional limitations is present after a shorter follow-up time in the oldest age group compared with the younger age group. (*J Clin Endocrinol Metab* 98: E1483–E1490, 2013)

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p16INK4a protects against dysfunctional telomere-induced ATR-dependent DNA damage responses.

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Abstract

Dysfunctional telomeres limit cellular proliferative capacity by activating the p53-p21- and p16INK4a-Rb-dependent DNA damage responses (DDR). The p16INK4a tumor suppressor accumulates in aging tissues, is a biomarker for cellular senescence, and limits stem cell function in vivo. While the activation of a p53-dependent DDR by dysfunctional telomeres has been well documented in human cells and mouse models, the role for p16INK4a in response to telomere dysfunction remains unclear. Here, we generated protection of telomeres 1b p16^{-/-} mice (Pot1b Δ/Δ ;p16^{-/-}) to address the function of p16INK4a in the setting of telomere dysfunction in vivo. We found that deletion of p16INK4a accelerated organ impairment and observed functional defects in highly proliferative organs, including the hematopoietic system, small intestine, and testes. Pot1b Δ/Δ ;p16^{-/-} hematopoietic cells exhibited increased telomere loss, increased chromosomal fusions, and telomere replication defects. p16INK4a deletion enhanced the activation of the ATR-dependent DDR in Pot1b Δ/Δ hematopoietic cells, leading to p53 stabilization, increased p21-dependent cell cycle arrest, and elevated p53-dependent apoptosis. In contrast to p16INK4a, deletion of p21 did not activate ATR, rescued proliferative defects in Pot1b Δ/Δ hematopoietic cells, and significantly increased organismal lifespan. Our results provide experimental evidence that p16INK4a exerts protective functions in proliferative cells bearing dysfunctional telomeres.

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REVIEWS

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Review Series

Potential applications for biguanides in oncology

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Metformin is widely prescribed for the treatment of type II diabetes. Recently, it has been proposed that this compound or related biguanides may have antineoplastic activity. Biguanides may exploit specific metabolic vulnerabilities of transformed cells by acting on them directly, or may act by indirect mechanisms that involve alterations of the host environment. Preclinical data suggest that drug exposure levels are a key determinant of proposed direct actions. With respect to indirect mechanisms, it will be important to determine whether recently demonstrated metformin-induced changes in levels of candidate systemic mediators such as insulin or inflammatory cytokines are of sufficient magnitude to achieve therapeutic benefit. Results of the first generation of clinical trials now in progress are eagerly anticipated. Ongoing investigations may justify a second generation of trials that explore pharmacokinetic optimization, rational drug combinations, synthetic lethality strategies, novel biguanides, and the use of predictive biomarkers.