ESSAY

TRANSLATIONAL MEDICINE

A target for pharmacological intervention in an untreatable human disease

Yeast and mouse studies identify the mechanistic target of rapamycin (mTOR) as a target for treatment of a mitochondrial disease.

By **Simon C. Johnson**

Mitochondrial dysfunction contributes to a variety of pathological conditions—including cardiovascular disease, diabetes, cancer, muscular disorders, and neurodegenerative disease. Defects in genes important for mitochondrial function can cause severe illness and lead to devastating and untreatable childhood diseases. Leigh syndrome, or subacute necrotizing encephalomyelopathy, is a clinically defined disease presenting with myopathy, lactic acidosis, dyspnea, and characteristic progressive lesions of the brain stem, cerebellum, and basal ganglia.

Encephalomyelopathy is the major defining feature of Leigh syndrome, ultimately leading to death from respiratory failure. Rate of progression varies, but death typically occurs by 6 to 7 years of age. Identifying viable treatment strategies in mitochondrial disease is a major translational research goal; viable interventions have significant potential for benefiting human health in both rare and common diseases.

My doctoral research began with a yeast genetic screen and, motivated by the results, led to an intervention study in a mouse model of Leigh syndrome (see the figure). Our objective with the yeast study was to investigate the relation between genetic background and response to caloric restriction (CR). CR, reduced caloric intake without malnutrition, is a dietary intervention that increases life span and reduces aging-related pathologies in eukaryotes from yeast to primates. Although the benefits of CR are well-established, the impact of genetic background on the response to CR was largely unexplored. Given that CR mimetics are widely considered to have substantial clinical potential for age-related disease, the impact of genetic modifiers is important to human health.

We examined a large set of yeast strains with mutations in single genes to determine the impact of genetic background on yeast replicative life-span (RLS) response to CR (*1*). We found that these strains show a great diversity in the direction and magnitude of change in RLS.

To describe the genotype-CR interaction, I used gene ontology to define processes associated with positive or negative CR responses. Ontology analysis revealed that strains with significantly decreased life span were enriched for genes in several biological processes, including vacuolar function, protein catabolism, and pH homeostasis. However, strains showing significant RLS increase during CR were enriched for only one category: mitochondrial function. Many of the associated genes involved in mitochondrial function are highly conserved, including homologs of genes associated with mitochondrial disease in humans. The robust effects of CR on yeast mitochondrial mutants led us to pose the question: Are the beneficial effects of CR in the setting of mitochondrial deficiency conserved in mammals? If so, pharmaceutical agents that mimic CR (CR mimetics) by modulating nutrient sensing could provide therapeutic options in mitochondrial disease. Although mammals are vastly more complex than yeast, the intracellular mechanisms regulating nutrient signaling are highly conserved, which suggests that the beneficial impact of CR could be conserved as well.

To answer this question, we examined the efficacy of rapamycin in the *Ndufs4*$^{-/-}$ mouse (*2*). Ndufs4 loss is associated with Leigh syndrome in humans, and the mouse knockout closely recapitulates the human disease, which includes subacute necrotizing encephalopathy and progressive neurological degeneration that result in early mortality. These mice are considered the premier model of mitochondrial disease, given the robust similarity to Leigh syndrome. Untreated, these mice live an average of 50 days, and maximum life span is about 80 days. Rapamycin inhibits the mechanistic target of rapamycin, mTOR, a central regulator of intracellular nutrient sensing and signaling. mTOR acts downstream of insulin–insulin-like growth factor 1, AMP-activated protein kinase, and amino acid sensing at the lysosome, and mTOR inhibitors are considered to be CR mimetics (*3*, *4*). We reasoned that if the benefits of CR are conserved in mammals, mTOR could provide a pharmacological target for intervention. A number of FDA-approved drugs targeting mTOR are used clinically, including rapamycin, so any benefit observed in mice could in theory be rapidly translated to clinical trials.

In this study, I found that rapamycin has a profoundly beneficial, dosage-dependent impact on disease onset and progression in

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Category Winner

Translational Medicine: Simon C. Johnson for his essay, "A target for pharmacological intervention in an untreatable human disease." Dr. Johnson is an American Federation for Aging Research Fellow at the Albert Einstein College of Medicine in New York. He earned his Bachelor of Science degree at Oregon State University and received his Ph.D. from the University of Washington. He was a 2009 Howard Hughes Medical Institute EXROP scholar and was previously supported by the Nathan Shock Center Genetic Approaches to Aging predoctoral and Mechanisms of Cardiovascular Diseases postdoctoral competitive training grants. His work is centered on characterizing the role of genetic variation in insulin/IGF-1/mTOR signaling genes on human longevity.

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the Leigh syndrome model. Daily subcutaneous injection of rapamycin resulted in a maximum life span that was increased by more than 300%, an unprecedented finding in a disease model where no effective interventions existed. Neurological disease symptoms were attenuated, with many animals dying without showing signs of advanced degeneration. Immunological staining indicated that the characteristic lesions present in 100% of vehicle-treated *Ndufs4*$^{-/-}$ mice were absent or greatly decreased in severity in rapamycin-treated animals, even at advanced age. Mechanistic studies revealed that the benefits of mTOR inhibition do not appear to be the result of immune modulation, rescued electron transport chain complex levels or assembly, or mitochondrial respiratory capacity. Rather, rescue was associated with a metabolic shift relieving the accumulation of metabolic intermediates in *Ndufs4*$^{-/-}$ brain. Furthermore, we found that mTOR signaling is hyperactivated in untreated *Ndufs4*$^{-/-}$ mice, an observation with dramatic implications for the pathogenesis of mitochondrial disease.

My thesis work has major implications in mitochondrial disease, aging research, and the use of yeast as a model for human biology. In mitochondrial disease, we identified a clinically relevant target for treatment, reporting an unprecedented rescue of disease. Our therapeutic strategy and our observation of increased baseline mTOR signaling may prove relevant to a broad range of mitochondrial disorders. The mouse study validated the relevance of findings from our yeast genetic screen and demonstrated that RLS and pathway analysis in yeast can be predictive of mammalian biology. These studies provide a clear example of how model organisms can provide insight into human disease biology and further the goals of translational research. ■

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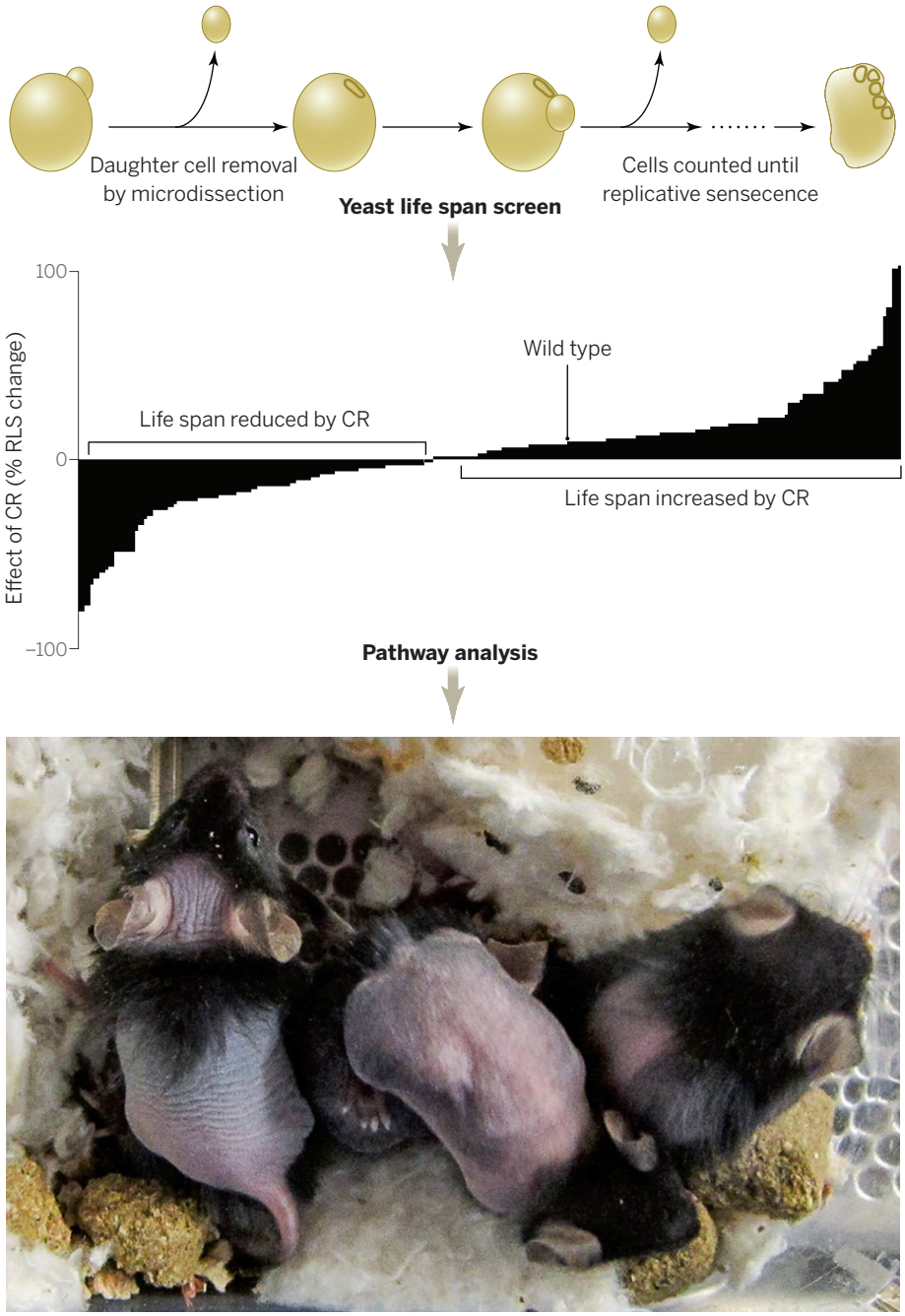

Pharmaceutical intervention in a mammalian model

From yeast to mammals—identifying a treatment strategy for mitochondrial disease. Yeast genetics provide a powerful tool that can yield mechanistic insight into disease and provide new targets for intervention.

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