Mi

yeast strain 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 encephalomyelopathy 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

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.

For the full text of all winning essays and further information, see http://scim.ag/SciLifeLab.

Published by AAAS
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.

REFERENCES

10.1126/science.aaa1811

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.
A target for pharmacological intervention in an untreatable human disease
Simon C. Johnson

Science 346 (6214), 1192.
DOI: 10.1126/science.aaa1811