New evidence links sirtuins and life extension

Study from Leonard Guarente shows how sirtuins act in the brain during calorie restriction to potentially lengthen lifespan.

Anne Trafton, MIT News Office

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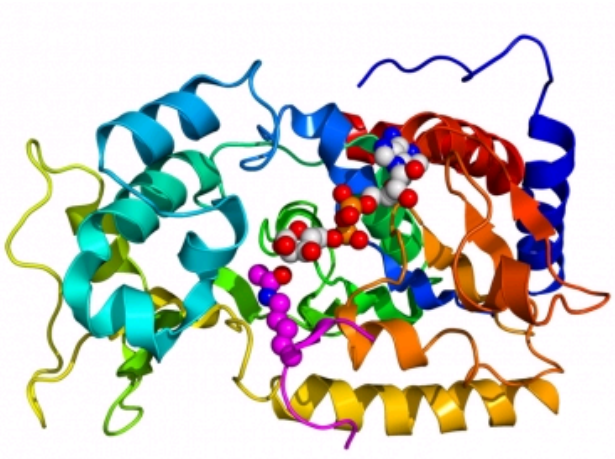

Crystallographic structure of yeast sir2 complexed with ADP and a histone H4 peptide containing an acylated lysine residue.

Ever since he first discovered the lifespan-extending effects of proteins called sirtuins 15 years ago, MIT Professor Leonard Guarente has been accumulating evidence to demonstrate a link between sirtuins and the effects of calorie restriction on lifespan.

For decades, it has been known that cutting normal calorie consumption by 30 to 40 percent can boost lifespan and improve overall health in animals such as worms and mice. Guarente believes that those effects are controlled by sirtuins — proteins that keep cells alive and healthy in the face of stress by coordinating a variety of hormonal networks, regulatory proteins and other genes.

In his latest work, published yesterday in the journal Genes and Development, Guarente adds to his case by reporting that sirtuins bring about the effects of calorie restriction on a brain system, known as the somatotropic signaling axis, that controls growth and influences lifespan length.

“This puts SIRT1 at a nexus connecting the effects of diet and the somatropic signaling axis,” says Guarente. “This is a major shot across the bow that says sirtuins really are involved in fundamental aspects of calorie restriction.”

Guarente and others believe that drugs that boost sirtuin production could help fight diseases of aging such as diabetes and Alzheimer’s, improving health in later life and potentially extending lifespan. Drugs that promote sirtuin production are now in clinical trials in diabetes patients, with results expected next year.

Making connections

Guarente decided to look into a possible connection between sirtuins and the somatotropic signaling system because it was already known that the system is influenced by calorie restriction. When food intake goes down, the hypothalamus slows down production of growth hormones, resulting in smaller, longer-lived animals.

In this study, Guarente and colleagues genetically engineered mice whose ability to produce the major mammalian sirtuin SIRT1 in the brain was greatly reduced. They fed those mice and a control group of normal mice a calorie-restricted diet. The normal mice showed much lower levels of circulating growth hormones, demonstrating that their somatotropic signaling system was being suppressed, but calorie restriction had no

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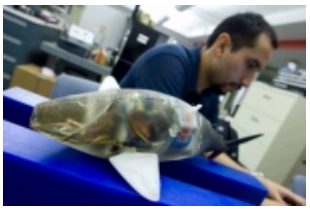

Valdivia y Alvarado, a research affiliate in the Department of Mechanical Engineering, works in his lab on a robotic fish he created with Professor Kamal Youcef-Toumi. The robot is designed to more easily maneuver into areas where traditional underwater autonomous vehicles cannot go.
Patrick Gillooly

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effect on hormone levels of mice that could not produce SIRT1.

The mice that could not produce SIRT1 also did not display any of the food-foraging behavior usually seen in mice put on a low-calorie diet.

Guarente has previously shown that calorie restriction boosts levels of a co-enzyme called NAD, which in turn activates SIRT1. That alone suggests a link between sirtuins and calorie restriction, he says, and the latest findings bolster the case.

David Sinclair, professor of pathology at Harvard Medical School and former postdoctoral associate in Guarente's lab, says the new study fills in an important missing piece of the sirtuin puzzle — how sirtuins act in the brain to mediate the effects of calorie restriction. "Until this paper, the focus has been on tissues like muscles and liver and other organs that control metabolism."

Sinclair is founder of a company, Sirtris, which was recently acquired by GlaxoSmithKline and is running clinical trials of sirtuin-boosting drugs.

While many scientists have embraced the idea that sirtuins are necessary to carry out the effects of calorie restriction, others are still unconvinced. Richard Miller, professor of pathology at the University of Michigan Medical School Institute of Gerontology, points out that the new study did not link SIRT1 knockout with shorter lifespan or declining health.

The relationship between sirtuins and longevity is "more complicated than people had hoped would be the case," says Miller, who believes sirtuins are likely one of many cell-signaling systems that influence aging.

Guarente says he believes someday the skeptics will be convinced. "Some people will never be convinced, because it seems too simple," he says. "But at some point, the weight of evidence will become such that most reasonable people will concur."

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There are other scientific documents to support sirtuins increase lifespan. Other Studies on sirtuins show that they are involved in metabolic regulation. They turn particular genes on and off as need. for example, and they also work to repair damage to the DNA. They are implicated in aging because as organisms age, the rick of damage to the DNA increases, and the sirtuins may become increasingly focused on addressing specific site of damage.