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Fast track to longevity

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Researchers have moved a step forward in understanding how calorie restriction is linked to lifespan extension in mammals. In this week's issue of *Nature* **,** a group from the United States reports that SIRT1 - the mammalian version of a protein linked to longevity in simpler organisms - controls glucose metabolism in mice in response to fasting.

Pere Puigserver of Johns Hopkins University and colleagues found that fasting signals induce the SIRT1 protein in the liver. This protein is one of the mammalian homologues of Sir2, known to extend lifespan in yeast and worms. SIRT1 then interacts with the coactivator PGC-1alpha, which, in turn, triggers glucose production, a key metabolic change associated with extended lifespan.

"Our work provides a novel connection between PGC-1alpha, a protein involved in the food-deprivation response, and SIRT1, a protein linked to aging in lower organisms," Puigserver told *The Scientist*.

SIRT1, which is an NAD^+-dependent histone deacetylase, had already been associated with calorie restriction and longevity in mammals. Induced by food deprivation, it inhibits stress-induced apoptotic cell death in vitro and promotes fat mobilization in vitro and in vivo. However, it was unclear how SIRT1 might be involved in pathways such as gluconeogenesis and glycolysis, which are directly affected by calorie restriction in mammals.

In the *Nature* paper, the research team provides a connection between SIRT1 and these pathways. Moreover, they show that SIRT1 acts as a sensor of food deprivation.

"During starvation, there is an increase in pyruvate, a nutrient signal that induces translation of SIRT1, and an increase in NAD^+, which functions as a substrate and as an activator of SIRT1. The active SIRT1 interacts with PGC-1alpha, deacetylates it, and keeps it active, promoting glucose production in the liver," explained Puigserver. With these results, the researchers showed that besides the hormonal control of PGC-1 through glucocorticoids and glucagon during fasting, there is a nutrient control as well, which targets SIRT1.

Marc Tatar of Brown University, who did not participate in the research, found the role of SIRT1 in nutrient sensing impressive. "There are hormonal inputs for sensing nutrients that are released systemically and circulate throughout the body," Tatar told *The Scientist*. "But what we are beginning to see is that there are also systems in which every cell can sense the nutrient condition in their own neighborhood and adjust their metabolism to their local nutrient conditions."

Tatar said this type of autonomous nutrient sensing could date back to times when organisms were only single celled and didn't have hormone signals. "These are probably the roots, and the reason that you find [this sensing system] in yeast, nematodes and mammals, is because it is very ancestral. We are looking at it in flies," said Tatar.

According to Leonard Guarente of the Massachusetts Institute of Technology, who was not involved in the study, the *Nature* paper provides a good example in which SIRT1 is influencing a key

physiological aspect of calorie restriction in a mammal. "Although this is not the first example, it's an important one," he said.

Guarente's group recently reported how SIRT1 influences fat mobilization in mammals. "In fat cells, the target that SIRT1 is acting on is the nuclear hormone receptor PPAR-gamma, a critical regulator of fat; in this system, it's PGC-1, which is a cofactor for PPAR-gamma. This suggests we are converging in a critical pathway here."

"Calorie restriction really mitigates many diseases. Once we understand these pathways, we can think about developing drugs that can intervene pharmacologically and have implications to specific diseases," explained Guarente. "The hypothesis linking low food to longevity and disease resistance through Sir2 is robust. The testing of the hypothesis is just beginning."

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