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Researchers uncover details about how dietary restriction slows down aging

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University of Washington scientists have uncovered details about the mechanisms through which dietary restriction slows the aging process. Working in yeast cells, the researchers have linked ribosomes, the protein-making factories in living cells, and Gcn4, a specialized protein that aids in the expression of genetic information, to the pathways related to dietary response and aging. The study, which was led by UW faculty members Brian Kennedy and Matt Kaeberlein, appears in the April 18 issue of the journal *Cell*.

Previous research has shown that the lifespan-extending properties of dietary restriction are mediated in part by reduced signaling through TOR, an enzyme involved in many vital operations in a cell. When an organism has less TOR signaling in response to dietary restriction, one side effect is that the organism also decreases the rate at which it makes new proteins, a process called translation.

In this project, the UW researchers studied many different strains of yeast cells that had lower protein production. They found that mutations to the ribosome, the cell's protein factory, sometimes led to increased life span. Ribosomes are made up of two parts -- the large and small subunits -- and the researchers tried to isolate the life-span-related mutation to one of those parts.

“What we noticed right away was that the long-lived strains always had mutations in the large ribosomal subunit and never in the small subunit,” said the study's lead author, Kristan Steffen, a graduate student in the

UW Department of Biochemistry.

The researchers also tested a drug called diazaborine, which specifically interferes with synthesis of the ribosomes' large subunits, but not small subunits, and found that treating cells with the drug made them live about 50 percent longer than untreated cells. Using a series of genetic tests, the scientists then showed that depletion of the ribosomes' large subunits was likely to be increasing life span by a mechanism related to dietary restriction -- the TOR signaling pathway.

“We knew that dietary restriction decreased TOR signaling, and that decreased TOR signaling reduced translation or protein production, but this was the first direct evidence that all three were acting in the same genetic pathway,” said Kennedy, an associate professor of biochemistry.

"The big question then became what’s happening in these translation-deficient cells to slow aging," added Kaeberlein, an assistant professor of pathology. "That’s when Vivian MacKay, a co-author on the study, had the idea to look at Gcn4."

Gcn4 is a specialized protein called a transcription factor, which helps transfer genetic information during cell growth. The protein is activated when a cell is starving for amino acids. What made Gcn4 interesting to the UW team was its unique mode of regulation.

"When ribosomes aren’t working at 100 percent capacity, most proteins are made less efficiently, but Gcn4 is different," explained Dr. MacKay, a research professor of biochemistry. "Sometimes, you actually get more Gcn4 produced even when everything else is going down. That's precisely what we found in the longer-lived yeast strains with mutations in the large subunit of the ribosome."

To make the link between Gcn4 and longevity, the scientists then asked

whether preventing the increase of Gcn4 would block life span extension. In every case, cells lacking Gcn4 did not respond as strongly as Gcn4-positive cells.

"The increased production of Gcn4 in long-lived yeast strains, combined with the requirement of Gcn4 for full life-span extension, makes a compelling case for Gcn4 as an important downstream factor in this longevity pathway," Kaeberlein said.

Although scientists don't yet know whether Gcn4 plays a similar role in organisms other than yeast, Kennedy points out that worms, flies, mice and humans all have Gcn4-like proteins that appear to be regulated in a similar way.

"The role of TOR and translation in aging is known to be conserved across many different species, so it's plausible that this function of Gcn4 is conserved as well," Kennedy said. Future research will be aimed at testing this hypothesis.

"Clearly TOR signaling is one component, and perhaps the major component, of the beneficial health effects associated with dietary restriction," said Kaeberlein. "The difficulty with TOR as a therapeutic target, however, is the potential for negative side effects. As we learn more of the mechanistic details behind how TOR regulates aging, we will hopefully be able to identify even better targets for treating age-associated diseases in people."

Source: University of Washington

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