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Researchers Uncover New Genes that Control Longevity

An effort to understand the molecular mechanisms that control aging has led Howard Hughes Medical Institute researchers and their colleagues to 10 new genes that regulate longevity in yeast. The studies also suggest a new model for how aging is slowed when caloric intake is restricted.

Molecular biologists Matt Kaeberlein, Brian Kennedy, Stanley Fields, and colleagues at the University of Washington, reported in the November 18, 2005, issue of the journal *Science* that by decreasing the function of nutrient-responsive pathways such as TOR and Sch9, the life span of yeast is extended. Fields is a Howard Hughes Medical Institute investigator at the University of Washington.

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— Stanley Fields

The results of the studies are important because they begin to provide an explanation for the "life extension" effect seen in laboratory animals when food is restricted. So the studies could offer new clues about the molecular mechanisms that living organisms employ when food is scarce, said Fields.

Although it seems counterintuitive, experiments showed long ago that severely restricting food intake leads to an increase in longevity - by as much as 40 percent—in some animals. Although the longevity phenomenon was well documented in laboratory animals, researchers remained unsure about how it happened.

Now, the experiments by Kaeberlein, Kennedy, Fields and their colleagues are uncovering some of the molecular pathways that are involved in controlling longevity in yeast, and thus probably in more complex organisms.

"Through a large-scale screening process we have identified a set of genes that slows aging in yeast." Kaeberlein explained. He and his colleagues are hoping to use that model to expand their understanding of longevity higher up

the evolutionary ladder, even into humans. “We speculate that it is important in higher organisms,” Fields added, since very similar genes are found in most other species, from worms to fruit flies, mice and humans.

The next step, Kaeberlein said, is to begin similar work in the nematode worm, *Caenorhabditis elegans*. After that, they hope to study the process in mice, and eventually in humans—all with the goal of understanding the aging process.

Although it is unlikely to happen soon, the discoveries may eventually identify targets that can be manipulated—perhaps by drug treatments—to alter the aging process, Fields said. One drug, rapamycin, is already known to impact one of these genetic pathways, but it has the dangerous side effect of disabling the immune system.

“We'd like to understand how aging occurs in yeast,” Fields added, because “even though yeast is a simple, single-cell organism, it's still capable of revealing mechanisms in the aging process. Similar genes may control aging in higher organisms, too.”

The two years of laboratory work, much of it done by Kaeberlein and Kennedy, were extraordinarily tedious, involving complex genetic and biochemical tests on a special collection of 4,800 strains of yeast cells developed by other scientists. Each yeast strain was engineered to be special, and different, by lacking a different gene.

One of the group's most challenging tasks involved segregating 564 yeast strains into three categories: short-lived, not long-lived, and long-lived. Such work involved careful examination of tens of thousands of individual yeast cells under the microscope, separating “daughter cells” from “mother cells,” and segregating strains according to longevity.

In yeast, aging is measured by counting “replicative life span,” the number of daughter cells produced by a given mother cell before senescence. In the experiments published in *Science*, researchers categorized cells as not long-lived if the mean life span was less than 26 generations. If the mean life span was less than 20 generations, those yeast strains were put in the short-lived category. Finally, if the mean life span was greater than 36 generations, then those strains were called long-lived.

In time, the researchers gradually sorted out some gene mutations that altered the life span of the cells. As a result, “ten new genes were identified that are connected to longevity, and six of them are implicated in a single pathway” in the cell's response to nutrition, Fields explained.

For example, one gene they identified, called *TOR1*, seems to regulate yeast's response to nutritional conditions. When the gene is mutated, and not working properly, the yeast undergo a starvation response similar to that of calorie-restricted cells - even when nutrients are abundant. The acronym TOR stands for “target of rapamycin.”

What's also clear is that these genes don't work alone. TOR and its relatives are active in networks. Fields and his colleagues are trying to identify and analyze other parts of such systems.

“Our hope is that this will lead us to the mechanisms involved in caloric restriction and life extension,” Kaeberlein said.