Starve a yeast, sweeten its lifespan

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Johns Hopkins researchers have discovered a new energy-making biochemical twist in determining the lifespan of yeast cells, one so valuable to longevity that it is likely to also functions in humans.

Their findings, published in the March 20 issue of *Cell*, reveal that making glucose is highly influenced by a large enzyme complex already known to fix damaged DNA, and which apparently affects yeast life span through a common chemical process—acetylation.

In a series of experiments, the Hopkins team showed that when continuously acetylated, the so-called NuA4 enzyme complex causes yeast cells to live longer than they would under normal conditions.

The team genetically modified yeast cells, designing one to mimic the constantly acetylated form of the enzyme and another to mimic the constantly de-acetylated form. Then they compared these two mutants to a cell in which nothing was genetically altered. They found that the constantly acetylated form of yeast cell can outlive the unaltered cell by 20 percent and that the constantly de-acetylated form had an 80 percent reduction in its lifespan compared to the unaltered cell.

"Because the NuA4 complex is highly conserved among species, what we've found in yeast translates to humans as well," explains Heng Zhu, Ph.D., an assistant professor of pharmacology and molecular sciences at the Johns Hopkins University School of Medicine. "What we've revealed about longevity in yeast perhaps someday can translate to human health," he added.

Using a yeast proteome chip — a glass slide containing 5,800 or more than 80 percent coverage of all of the yeast-encoded proteins — the researchers hunted along this string of proteins to find specific molecular targets of the NuA4 complex.

By analyzing the yeast proteome chip and noting which proteins had an acetyl group stuck to them after adding NuA4, the team identified more than 90 such possible targets. To figure out which of these would naturally be acetylated, the team chose a random set of 20 to test further, ultimately confirming 13 as targets of the NuA4 complex.

More than simply expanding the list of known targets from three to 13, the team provided the first evidence that acetylation controls the activity of an enzyme called Pck1p, critical to sugar production in yeast and probably human cells. This enzyme is also controlled by the enzyme Sir2, which removes the acetyl group. Sir2 is heavily implicated in aging and a number of diseases by recent studies in mammals.

"The new function we identified for Pcklp is regulation of glucose-making, which is what all cells do to survive under conditions of starvation," Zhu explains.

Funded by the National Institutes of Health Roadmap Program, this interdisciplinary study involving biochemistry, proteomics, genetics and computational biology is a product of the High Throughput Biology Center, or HiT Center, of Johns Hopkins' Institute for Basic Biomedical Sciences.

Source: Johns Hopkins Medical Institutions

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