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Researchers Find Link Between Cell's Energy Use and Genome Health

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While studying how a cell keeps its genetic material intact, scientists at Johns Hopkins got busy alternately knocking out two catalysts vital to managing a yeast cell's energy. They discovered to their complete surprise that the removal of one of them led the cell to turn off 70 percent of its 5,000 genes and die.

"We were completely unprepared for such a dramatic event," says Jef Boeke, Ph.D., Sc.D., a professor of molecular biology and genetics at Hopkins and author of the study. "We've never seen anything that can turn off that many genes in a cell at once."

The unexpected finding linking both gene usage and energy management machinery is "like finding out that an enzyme that breaks down food in the stomach also helps you remember telephone numbers or that preventing such digestion makes you forget them," Boeke added.

The research, to be published in the July 21 issue of *Molecular Cell*, could lead to new strategies one day to slow aging and treat cancer, events closely linked to changes in gene control and energy metabolism.

Working at the High Throughput Biology Center of the Institute for Basic Biomedical Sciences at Hopkins, Boeke's team uses yeast almost exclusively for such studies because even though they are single-celled organisms, they grow quickly, are easy to analyze in the lab, and contain many genes and biological processes present in other animals, including humans.

For example, like all animal cells, yeast use sugar as an energy source. To harvest the energy contained in sugar, the yeast must convert the sugar into other molecules in a series of biochemical steps helped along the way by enzymes that make each step happen faster.

Focusing on two of these enzymes, closely related to each other, the research team separately removed each from the yeast cells to see if either or both were essential to the cell's survival.

The researchers found that one of these enzymes – called Acs1p – which is generally inactive had little apparent impact when they removed it. "The yeast seemed relatively unscathed," said Boeke.

But when they knocked out the other one – called Asc2p – the yeast cells died. That made it clear that this enzyme is critical for survival.

Further analysis with high-power microscopes revealed that this second enzyme, Asc2p, was residing – unexpectedly -- in the part of the cell housing its genetic material – its chromosomes – rather than in the part of the cell – the mitochondria -- that harvests energy from sugar.

But why would an enzyme involved in generating energy live in the "wrong" part of the cell? A closer look at the chromosomal and non-chromosomal parts of the cell showed that although the enzyme itself is found only in the former, the chemical made by it is found in both places.

The question remained as to why the enzyme Asc2p and its chemical product, known as acetyl-CoA, are found near chromosomes.

Chromosomes contain both DNA, which contains genes, and proteins around which the DNA is wrapped for storage and support.

In addition to being used for energy, the acetyl part of acetyl-CoA also is used in controlling how tightly DNA is wrapped in the chromosomes. More acetyl on chromosomes leads to looser wrapped DNA. And locations along chromosomes that contain looser wrapped DNA appear to be regions where genes are turned on.

When the research team removed the enzyme Asc2p that makes acetyl-CoA from yeast cells, they predicted, if they were right about why the enzyme and its chemical product are found near chromosomes, that the chromosomes would have less acetyl-CoA. Less acetyl-CoA, they reasoned, could cause DNA to be more tightly wrapped in chromosomes, and this might lead to genes being turned off. That is exactly what they found when they looked at the more than 5,000 genes in the yeast cells lacking this enzyme. More than 70 percent of them were indeed turned off.

According to Boeke, other studies have shown that reducing the number of calories a yeast cell “eats” not only can affect chromosomes, but also increase lifespan, allowing the yeast to live longer, an observation that fits their findings.

Source: Johns Hopkins Medical Institutions