

## Vitamin extends life in yeast, researchers find

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Imagine taking a vitamin for longevity! Not yet, but a Dartmouth discovery that a cousin of niacin prolongs lifespan in yeast brings the tantalizing possibility a step closer.

The research, reported in the May 4 issue of *Cell*, shows how a new vitamin extends lifespan in yeast cells, much like calorie restriction does in animals. It could pave the way for developing supplements to benefit humans.

Radical calorie reduction can extend life. Dieting or fasting mice live longer and lowering the glucose that yeast grow on extends their lifespan, according to Dr. Charles Brenner, associate professor of genetics and of biochemistry, who led the research.

“If we could do this in humans -- give people a drug or vitamin that would mimic effects of calorie restriction without having to skip lunch -- we would be able to provide some of the benefits of calorie restriction, which are pretty striking in model organisms,” said Brenner, also a member of the Norris Cotton Cancer Center at Dartmouth-Hitchcock Medical Center.

Many benefits, explains Brenner, depend on a family of proteins called sirtuins—dubbed anti-aging gene products for the important roles they play in longevity and energy expenditure, although the precise mechanisms are still being figured out.

His team found that providing a newly discovered vitamin activates the yeast anti-aging gene product Sir2, which resembles sirtuins found in humans. The new work builds on Brenner's prior discovery of the vitamin, termed NR (nicotinamide riboside), a natural product found in milk. Like the B3 vitamin, niacin, NR is a precursor to a versatile cellular factor that is vital for all life.

The factor, called NAD, short for nicotinamide adenine dinucleotide, is elevated by calorie restriction. So the researchers set out to develop an intervention to elevate NAD, using yeast cells, whose genes are easy to manipulate. "It's surprising that no one was able to elevate NAD with a small molecule before," Brenner said.

The team discovered two pathways that allow yeast to raise NAD levels with NR, improve their control of gene expression and live longer in the presence of high glucose. One of the pathways is new; the other was previously identified by Brenner's lab.

At the molecular level, elevating NAD to turn on Sir2 actually enables the yeast to silence genes that are not supposed to be expressed. In any organism, not all genes are on at once; in yeast, there are sets of genes that Sir2 normally represses.

"We showed that that we could improve Sir2-dependent gene silencing with NR and increase the longevity of yeast grown in high glucose conditions," Brenner said.

To test for Sir2 gene repression, the investigators found conditions in which wild-type cells can't accomplish normal gene silencing. Then, when they take up NR through one of the pathways Brenner's team discovered, Sir2 gene silencing is restored, and yeast are rejuvenated. Yeast cells formerly capable of dividing 13 times, divided over 23 times when given NR.

Deletion of either pathway makes NR only half as effective as it is when both pathways are intact. So yeast cells seem to use both pathways equally well to lengthen their lifespan. The first NR pathway, described in 2004, consists of a gene common to yeast and humans. In fact, that gene is activated in damaged neurons in order to allow NR to protect against loss of axons. The second NR pathway involves three yeast genes, two of which are found in humans.

Granted that the human anti-aging apparatus is more complex, but animal studies indicate potential. Perhaps the best known sirtuin activator is the red wine compound resveratrol. Overfed mice on high dose resveratrol have healthier livers, better endurance and possibly longer lifespan. While resveratrol and NR work through different mechanisms to increase sirtuin activity, Brenner said, “the two compounds could be complementary or synergistic.”

More testing remains for NR in humans, but Brenner foresees intriguing possibilities. “As a natural product found in milk, we expect the compound to be much safer than most drugs, and to be a more specific remedy than most vitamins.”

Though aging itself is not a disease, Brenner anticipates applications in conditions associated with aging including neurodegenerative diseases, metabolic syndrome, and elevating good cholesterol. There are also indications that NR could be a treatment for one type of Candida infection.

Source: Dartmouth Medical School

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