Discovery may aid search for anti-aging drugs

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A team of University of Michigan scientists has found that suppressing a newly discovered gene lengthens the lifespan of roundworms. Scientists who study aging have long known that significantly restricting food intake makes animals live longer. But the goal is to find less drastic ways to achieve the same effect in humans someday. The U-M results offer promising early evidence that scientists may succeed at finding targets for drugs that someday could allow people to live longer, healthier lives.

In a study in the August issue of *Aging Cell*, U-M scientists found that a gene, drr-2, is an important component in a key cellular pathway, the TOR nutrient-sensing pathway, where many scientists are looking for potential drug targets. The U-M scientists then found that when they caused the drr-2 gene to be under- or over-expressed, they could lengthen or shorten lifespan in *C. elegans*, a worm widely used in research. Manipulating the drr-2 gene's action produced the same effects as reducing or increasing caloric intake.

"We showed that in *C. elegans*, drr-2 is one of the essential genes for the TOR pathway to modulate lifespan," says Ao-Lin Allen Hsu, Ph.D., the study's senior author and a scientist at the U-M Geriatrics Center. He also is an assistant professor in internal medicine and molecular and integrative physiology at U-M. The study also found that drr-2 appears analogous to a human gene, eIF4H, that controls similar cell functions.

Context

To find possible avenues for future anti-aging drugs, many scientists around the world are focusing on signaling pathways in cells that sense nutrients. The one Hsu examined, the target of rapamycin pathway or TOR pathway, is so named because its activity can be influenced by the drug rapamycin. Recent results from a large federal study being conducted at U-M and elsewhere have shown that in mice, rapamycin is effective at mimicking the anti-aging effects of dietary restriction.

Research in the last 25 years has shown that animals, including mammals, live longer and have lower levels of certain measures of age-related decline when scientists have restricted their food intake. No one has been able to show yet that the same effect happens in humans, though some studies are under way.

When calories or certain nutrients are restricted, scientists detect less oxidative damage in animal cells and a slower decline in DNA repair, a decline that normally occurs with age. It's thought that limiting oxidative damage and slowing the decline in DNA repair could help postpone or avoid many age-related diseases.

But scientists know relatively little about why reducing food intake causes these effects. In the last 10 years, they have made progress in identifying genes and associated proteins that are suppressed when diet is restricted. By learning more about the cell processes involved, they may be able to discover targets for future drugs that could delay aging without the need to restrict food intake.

Drugs tailored to block specific genes or proteins involved in nutrient-sensing pathways would have much more appeal than reducing what one eats. To achieve anti-aging benefits, it's thought that people would have to restrict food intake by 30 to 40 percent, a grim prospect. In addition, drugs might be designed to avoid other disadvantages of this level of dietary restriction, which include reduced fertility.

C. elegans is a tiny roundworm, a nematode whose two-week lifespan is a great advantage for scientists studying aging. The 1-millimeter-long transparent worms have other advantages, too. *C. elegans* exhibits many age-associated changes observed in higher organisms.

"Many genes identified in *C. elegans* to control the speed of aging turned out to be evolutionarily conserved, meaning that you can find them in other animals, too. And many are very similar to those found in humans," Hsu says.

Research details

Hsu and his team created different mutant strains of roundworms, some with drr-2 genes silenced and others in which the gene was over-expressed. They wanted to learn whether inactivating drr-2 is essential for TOR to influence longevity, and found that it was. Other newly discovered genes may affect TOR signaling as well. But Hsu's team has found a promising lead for anti-aging drugs of the future: They were able to show that silencing drr-2's action alone was sufficient to make worms live longer than wild-type *C. elegans* used as controls.

"It is known that reduction of TOR signaling in response to a change in the environment or genetic manipulation triggers a cascade of cellular signals that alter cell growth, metabolism, and protein synthesis, and decrease the pace of aging," says Hsu. "Our recent studies have shown that drr-2 might play a pivotal role in the TOR signaling network to control protein synthesis as well as longevity."

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