

New 'longevity gene' spurs hopes of long life

by Bend_Weekly_News_Sources

In studies dating back 70 years, mice and many other species subsisting on a near-starvation diet have consistently lived as much as 40 per cent longer than normal. But just why has been unclear.

Now, researchers at the Salk Institute for Biological Studies in La Jolla, Calif., report they have cracked the riddle, finding the first gene that specifically links this 'caloric restriction' regimen to longevity. "We finally have genetic evidence to unravel the underlying molecular program required for increased longevity in response to caloric restriction," said the institute's Andrew Dillin, who led the study published online in the May 2 issue of the journal *Nature*. The finding opens the door to development of drugs that mimic caloric restriction effects, he added. These could allow people to reap health benefits without going hungry. One compound that may fit this description, resveratrol, is already marketed and has shown promise in animal studies. But it's not clear whether it acts specifically on the biochemical pathway of dietary restriction—one of three separate pathways known to affect longevity, Dillin said. Caloric restriction also is the only strategy apart from direct genetic manipulation that consistently prolongs life in animals, Dillin noted. It also cuts the risk of cancer, diabetes, and cardiovascular disease and staves off age-related neurodegeneration in laboratory animals from mice to monkeys. The price: caloric restriction requires cutting to around 60 per cent of normal calories intake while maintaining a healthy diet rich in vitamins, minerals, and other nutrients, Dillin said. Although some people live by this regimen, it's too soon to say whether it will extend life span in humans, Dillin said. In the quest for genes involved in the caloric restriction response, graduate student Suzanne Wolff and others in Dillin's laboratory studied an array of genes related to ones previously linked to anti-aging pathways. They found that only one gene, called pha-4, specifically affected the caloric restriction response. In roundworms, they reported that loss of the gene, and the protein molecule whose production it encodes, negated caloric restriction's life-extending effect. Stimulating it enhanced the effect. Dillin speculated that the longevity benefits of near-starvation may have evolved as a system to help animals live through stressful times. Pha-4 "may be the primordial gene that regulates nutrient sensing and helps animals live a long time through stress and dietary restriction," he added. One other gene, called sir-2, has been implicated in the life- and health-prolonging response to caloric restriction, Dillin said. But while loss of sir-2 disrupts the caloric restriction response only in yeast, it has no effect on other organisms, such as worms, Dillin added. Resveratrol is proposed to stimulate sir-2. Besides caloric restriction, the two other molecular pathways affecting longevity are called the insulin/IGF signaling and the mitochondrial electron transport chain pathways, Dillin said. "It is still not clear where sir-2 fits in. It seems to meddle with more than one pathway," he added. "PHA-4 is specific for caloric restriction as it does not affect the other pathways." Humans have three genes very similar to worm pha-4; they all belong to a family of genes called Foxa, Dillin continued. All three play roles in development and later in the regulation of glucagons, a pancreatic hormone that unlike insulin boosts blood sugar levels and maintains energy balance, especially during fasting. Scientists might be able to exploit the findings to create anti-aging treatments "specifically, by finding ways to stimulate Foxa activation," researchers said. "Those are experiments we're actively collaborating on," said Siler Panowski, a graduate student in Dillin's laboratory.

Courtesy Salk Institute and World Science staff

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