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Low-Calorie Diet Slows Aging in Mice in Study

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Putting elderly mice on a very low-calorie diet for as little as four weeks reversed many of the changes in the activity of various genes that had occurred during normal aging, according to a new study.

The research, which used a new technology to pinpoint which genes are active in mice at different ages, may help scientists to understand how calorie restriction extends animals' lifespan and, eventually, to develop longevity therapies for humans.

"My work shows that calorie restriction not only prevents [age-related] changes" in gene activity, "but very quickly reverses the majority of the changes that take place with age," said Stephen R. Spindler, a professor of biochemistry at the University of California at Riverside and an author of the study.

Huber Warner, associate director of the biology of aging program at the National Institute on Aging, said the results were interesting but needed to be confirmed. Until recently, he said, scientists have been able to examine aging's effects on relatively few genes, but the new technology allows a "vast number of genes [to] be looked at" simultaneously.

Severe calorie restriction is the only treatment that consistently has been shown to extend mammals' lifespan, although its effectiveness in people is unproven. In animals, it lowers the incidence of cancer and delays the onset of other age-related diseases. Although scientists have theorized that low-calorie diets may reduce age-related cell damage and decrease levels of cancer-promoting growth factors, they have only recently been able to examine how such diets affect the function of many of the approximately 30,000 genes present in a mouse or a person.

Spindler and colleagues used a method called microarray technology to analyze which of 11,000 different genes were expressed -- or used to provide instructions for making proteins -- in the livers of young and old mice. They also tested the effect of calorie restriction on gene expression. Some mice were fed a low-calorie diet -- providing just enough food to prevent starvation -- from the time they were weaned, and others were switched from a normal to a low-calorie diet for four weeks starting when they were 34 months old.

In microarray technology, chemical probes for identifying the instructions from various genes are laid out in a checkerboard array on a silicone chip. Scientists isolate messenger RNA -- the chemical that carries instructions from genes -- from the cells they wish to study and apply it to the chip. When a gene is being expressed, the instructions from that gene bind to the corresponding probe and make it light up. The light signal is analyzed by a computer.

The scientists found 20 genes whose expression increased with age. Several were associated with inflammation, a process that in the liver can contribute to the development of cirrhosis or cancer. Others were genes involved in protecting and repairing cells and in preventing cell suicide. In 14 of the 20 genes, long-term calorie restriction completely or partially prevented the age-related changes.

The expression of 26 other genes decreased with age. Some of those were normally responsible for putting the brakes on cell growth and division, and an age-related reduction in their activity could explain why mice of the strain studied often die of cancer. Some other affected genes were responsible for detoxifying foreign substances such as drugs. Long-term calorie restriction partially reversed the age-related changes in 13 of the 26 affected genes.

Switching mice to the low-calorie diet at 34 weeks of age reproduced about 70 percent of the effect of keeping animals on a low-calorie diet lifelong, Spindler said. That suggests that if there are health benefits of calorie restriction in humans, some of those benefits could be obtained by reducing calories even in old age.

Spindler said he hopes to develop the technique for studying gene activity and use it to screen other potential anti-aging treatments. He said he is chief scientific officer and a stockholder of a company, LifeSpan Genetics, which holds a patent on the testing method. However, he added, funding for the study came from a nonprofit foundation. It was published in the Sept. 11 issue of the journal Proceedings of the National Academy of Sciences.

Spindler emphasized that it is likely to take years for researchers to determine what the various age-related changes in gene expression mean and which genes might be targets for therapies to retard aging. "It's hard to infer what the long-term consequences of any of those changes will be," he said. "But we're going to find out."