

Researchers Find Clues to the Mechanism of Aging

By: Madeline Ellis

Published: Monday, 1 December 2008



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Through the years, many people have searched for antidotes to the ravages of aging. In ancient China, Emperor Qin Shi Huang searched for the “elixir of life,” a universal medicine supposedly containing a recipe for the renewal of youth, and in 1513, Ponce de Leon set out to find the Fountain of Youth, a legendary spring whose waters could heal the sick and give everlasting life. Today, researchers continue the search for life-preserving medicines, but rather than exploring foreign lands, they are turning to the genetic intricacies of the human body to find them. As yet, they’ve had little success, but an unexpected discovery by Harvard Medical School scientists may provide critical clues to the mechanism of aging and, in time, lead to ways to prevent it.

Over the years, scientists have learned that members of a family of cellular enzymes known as sirtuins play critical roles in a wide range of vital life processes, including aging and gene expression. In 1991, a team of researchers led by David Sinclair in the

Massachusetts Institute of Technology lab of Leonard Guarente discovered that a sirtuin-type protein in yeast, roundworms, and fruitflies—Sir2—affected the aging process in two specific ways; it helped regulate gene activity in cells and repair DNA damage. “It’s looking like these sirtuins serve as guardians of the cell,” said David Sinclair, commenting on his teams’ study published in 2003 in the journal *Nature*. “These enzymes allow cells to survive damage and delay cell death.”

When the yeast cell is young and DNA damage is minimal, Sir2 was able to do both tasks. However, over time, as DNA damage accumulated, Sir2 became too preoccupied with repairs to properly regulate which genes were switched on and which were turned off. The decrease in the cell’s ability to detect patterns of gene expression resulted in aging.

In the new study, Philipp Oberdoerffer, a postdoctoral scientist in Sinclair’s Harvard Medical School lab, found that the same biochemical mechanism that makes yeast grow old works the same way in mice. The mouse version of Sir2, called SIRT1, also has dual roles; but its primary function is to help dictate how genes are expressed in various tissues. When the researchers treated mouse embryonic stem cells with DNA-damaging hydrogen peroxide, SIRT1 left its regulatory posts and migrated to the areas where DNA strands had broken. As a result, gene expression patterns went awry, with genes that were normally turned off becoming active, and vice versa. The researchers found that a number of these unregulated genes were persistently active in older mice. “One idea of why we age is that DNA becomes damaged or mutated,” said Sinclair, senior author of the new study. “But perhaps the main culprit is the effect of genes switching on and off, and that should be reversible.”

The team also found that mice with an excess of SIRT1 had an improved ability to repair DNA and prevent unwanted changes in gene expression. The hope is that those improvements could be reproduced with a drug that stimulates SIRT1. “In principle, we now could have a way of reversing the effects of aging,” said Sinclair, who also co-founded Sirtris Pharmaceuticals in Cambridge, Massachusetts, to investigate the therapeutic possibilities of resveratrol-based drugs. [Resveratrol](#), a compound found in grapes and red wine, works by activating sirtuins. It has been shown to prevent cardiovascular diseases, reduce heart inflammation, enable stronger bones and prevent eye cataracts. The company is reportedly testing a series of products, including a treatment for treating type 2 diabetes.

“What this paper actually implies is that aspects of aging may be reversible,” said Sinclair. “It sounds crazy, but in principle it should be possible to restore the youthful set of genes, the patterns that are on and off.”

The findings appear in the journal *Cell*.

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