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## SCIENTISTS FIND WHAT TYPE OF GENES AFFECT LONGEVITY

Tracing all the genetic changes that flow from a single mutation, UCSF scientists have identified the kinds of genes and systems in the body that ultimately allow a doubling of lifespan in the roundworm, *C. elegans*. Humans share many of these genes, and the researchers think the new findings offer clues to increasing human youthfulness and longevity as well.

Using DNA microarray technology, the researchers found that the single life-extending mutation – a change in the gene known as *daf-2* -- exerts its influence through antimicrobial and metabolic genes, through genes controlling the cellular stress response, and by dampening the activity of specific life-shortening genes.

"This study tells us that there many genes that affect lifespan, each on its own having only a small effect," said Cynthia Kenyon, PhD, UCSF professor of biochemistry and senior author on a paper in *Nature* reporting the research.. "The beauty of the *daf-2* gene is that it can bring all of these genes together into a common regulatory circuit. This allows it to produce these enormous effects on lifespan." Kenyon is also director of the Hillblom Center for the Biology of Aging at UCSF's Mission Bay campus.

Lead author on the paper is Coleen Murphy, PhD, a post-doctoral scientist in Kenyon's lab.

By partially disabling one gene at a time, either in *daf-2* mutants or in wild-type worms, through a technique known as RNA interference, the scientists were able to discover that no single gene by itself determines lifespan . Of the key genes, each can increase lifespan by 10 to 30 percent, the research shows. But when *daf-2* engages the whole army of genes, they can produce huge changes in lifespan.

Because any individual gene appears to have a relatively small effect on lifespan, identifying the key players would have been difficult in a standard genetic screen, the scientists say, underscoring the power of DNA microarray analysis for teasing apart complex systems.

Kenyon's team discovered ten years ago that a single mutation in the *daf-2* gene, which encodes a hormone receptor similar to the human receptors for the hormones insulin and IGF-1, doubled the worms' lifespan. The same or related hormone pathways have since been shown to affect lifespan in fruit flies and mice, and therefore are likely to control

(more)

lifespan in humans as well. Her lab found that *daf-2* affects lifespan through a second gene, known as *daf-16*, whose function was known to control the expression of other genes.

But the finding left unanswered just how longevity is achieved. What are the genes that *daf-16* regulates? The new research shows that several key systems are involved. Many of the genes that affect lifespan code for antioxidant proteins, the researchers found; others code for proteins called chaperones that help repair or degrade damaged proteins. This is especially interesting, Kenyon says, because many diseases of aging involve oxidative damage or protein aggregation.

Other longevity genes found active in the long lived mutants make proteins that help ward off bacterial infections, the researchers found. Kenyon's lab showed earlier that infections are the likely cause of death for the worm, recent research from others has shown that the long-lived animals are known to be resistant to bacterial infection. The current study shows that without these genes activated, the long-lived worms die sooner. In humans, too, infections pose a serious health problem for the aged.

"Maybe one day we will be able to tweak the insulin/IGF-1 systems in humans to produce many of the same benefits that we see in the worm," Kenyon says.

The scientists also found longevity genes affecting lipid transport and energy metabolism, as well as a host with unknown functions.

"The diversity of these lifespan gene functions is just remarkable" said Kenyon.

The long-lived worms, as well as mice with similar changes in the same genes, also are disease resistant, and the study suggests possible mechanisms for this finding. The antimicrobial response could protect against infections, and the antioxidant response can protect against diseases that involve oxidative damage. Many researchers suspect stroke and a number of neurological diseases in humans are hastened by oxidative damage.

Earlier this year, Kenyon's lab showed in *C. elegans* that the damage-repairing chaperone proteins not only increase lifespan, but also delay the onset of protein-aggregation diseases similar to Huntington's diseases.

"The marvelous thing about this new study is that it provides an explanation not only for the remarkable longevity of these animals, but also for their ability to stay healthy so long," Kenyon says.

"They just turn up the expression of many, many different genes, each of which helps out in its own way. The consequences are stunning, and if we can figure out a way to copy these effects in humans, we might all be able to live very healthy long lives," she adds.

Co-authors on the *Nature* paper are Cornelia Bargmann, PhD, professor of anatomy and Howard Hughes Medical Institute investigator at UCSF; Steven McCarroll, a graduate student; Hao Li, PhD, UCSF assistant professor of biochemistry; and Andrew Fraser and Ravi Kamath at the Wellcome CRC Institute and Department of Genetics, University of Cambridge.

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