Living longer, not healthier

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The worm C. elegans

A study of long-lived mutant *C. elegans* by scientists at the University of Massachusetts Medical School shows that the genetically altered worms spend a greater portion of their life in a frail state and exhibit less activity as they age then typical nematodes. These findings, published in the *Proceedings of the National Academy of Sciences*, suggest that genes that increase longevity may not significantly increase healthy lifespan and point to the need to measure health as part of aging studies going forward.

"Our study reveals that if we want to find the genes that help us remain physically active as we age, the genes that will allow us to play tennis when we're 70 similar to when we were 40, we have to look beyond longevity as the sole criteria. We have to start looking at new genes that might play a part in 'healthspan.'" said Heidi A. Tissenbaum, PhD, professor of molecular, cellular & cancer biology and the program in molecular medicine at UMass Medical School, and principal investigator of the study.

Genomic and technological advances have allowed scientists to identify several groups of genes that control longevity in *C. elegans*, a nematode used as a model system for genetic studies in the lab, as well as in yeast and flies. These genes, when examined, have analogs in mammals. The underlying assumption by scientists has always been that extending lifespan would also increase the time spent by the organism in a healthy state. However, for various reasons, most studies only closely examine these model animals while they're still relatively young and neglect to closely examine the latter portion of the animals' lives.

Challenging the assumption that longevity and health are intrinsically connected, Dr. Tissenbaum and colleagues sought to investigate how healthy long-lived *C. elegans* mutants were as they aged.

"The term healthspan is poorly defined in the lab, and in *C. elegans* few parameters have been identified for measuring health," said Tissenbaum. "So we set out to create a definition of healthspan by identifying traits that could be easily verified and measured as the worms aged."

Identifying both frailty and movement as measureable physical attributes that declined in the nematode with age and that could be tested, Ankita Bansal, PhD, now a postdoctoral scientist at the University of Pennsylvania, took four different *C. elegans* mutant specimen (daf-2, eat-2, ife-2 and clk-1) known to live longer than typical nematodes and measured their resistance to heat stress, oxidative stress and activity levels on solids and in liquids as they aged.

When Tissenbaum and her colleagues, Dr. Bansal; Kelvin Yen, PhD, now assistant research professor at the University of Southern California; and Lihua Julie Zhu, PhD, research associate professor of molecular, cellular & cancer biology at UMMS, compared these results with wild-type nematodes they found that all the animals—wild-type and mutants—declined physically as they aged. And depending on the

mutant specimen and trait being measured, each declined at different rates. Overall they found that the mutant worms, despite having longer lifespans, spent a greater percentage of their lives at less than 50 percent of measured maximum function when compared to wild-type nematodes. The increased lifespan experienced by the mutants was spent, instead, in a frail and debilitated state.

"What this means, is that the mutant nematodes were living longer, but most of that extra time wasn't healthy time for the worm," said Tissenbaum. "While we saw some extension in health as the mutants aged for certain traits, invariably the trade off was an extended period of frailty and inactivity for the animal. In fact, as a percentage of total lifespan, the wild-type worms spent more time in a healthy state than the long-lived mutants."

The implication for scientists, according to Tissenbaum, is that the set of genes that influence longevity may be distinct from the genes that control healthspan. "This study suggests that there is a separate and unexplored group of genes that allow us to perform at a higher level physically as we age. When we study aging we can no longer look at lifespan as the only parameter; we also have to consider health as a distinct factor of its own."

More information: Uncoupling lifespan and healthspan in Caenorhabditis elegans longevity mutants, Ankita Bansal, E277–E286, *PNAS*, DOI: 10.1073/pnas.1412192112

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