Combining mutants results in five-fold lifespan extension in C. elegans

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What are the limits to longevity? New research in simple animals suggests that combining mutants can lead to radical lifespan extension. Scientists at the Buck Institute combined mutations in two pathways well-known for lifespan extension and report a synergistic five-fold extension of longevity in the nematode *C. elegans*. The research, done at the Buck Institute and published online in *Cell Reports* on December 12, 2013, introduces the possibility of combination therapy for aging and the maladies associated with it.

The mutations inhibited key molecules involved in insulin signaling (IIS) and the nutrient signaling pathway Target of Rapamycin (TOR). Lead scientist and Buck faculty Pankaj Kapahi, PhD, said single mutations in TOR (in this case RSKS-1) usually result in a 30 percent lifespan extension, while mutations in IIS (Daf-2) often result in a doubling of lifespan in the worms – added together they would be expected to extend longevity by 130 percent. "Instead, what we have here is a synergistic five-fold increase in lifespan," Kapahi said. "The two mutations set off a positive feedback loop in specific tissues that amplified lifespan. Basically these worms lived to the human equivalent of 400 to 500 years."

Kapahi said the research points to the possibility of using combination therapies for aging, similar to what is done for cancer and HIV. "In the early years, cancer researchers focused on mutations in single genes, but then it became apparent that different mutations in a class of genes were driving the disease process," he said. "The same thing is likely happening

in aging." Kapahi said this research could help explain why scientists are having a difficult time identifying single genes responsible for the long lives experienced by human centenarians. "It's quite probable that interactions between genes are critical in those fortunate enough to live very long, healthy lives."

Former Buck postdoctoral fellow Di Chen, PhD, now an associate professor at the Model Animal Research Center, Nanjing University, China, lead author of the study, said that the positive feedback loop (DAF-16 via the AMPK complex) originated in the germline tissue of worms. The germline is a sequence of reproductive cells that may be passed onto successive generations. "The germline was the key tissue for the synergistic gain in longevity – we think it may be where the interactions between the two mutations are integrated," Chen said. "The finding has implications for similar synergy between the two pathways in more complex organisms."

Kapahi said ideally the research would move into mice as a way of determining if the lifespan-extending synergy extends into mammals. "The idea would be to use mice genetically engineered to have suppressed insulin signaling, and then treat them with the drug rapamycin, which is well-known to suppress the TOR pathway."

More information: "Germline Signaling Mediates the Synergistically Prolonged Longevity by Double Mutations in daf-2 and rsks-1 in C. elegans"; publishing online December 12, 2013 in *Cell Reports*.

Provided by Buck Institute for Age Research

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