Simple flip of genetic switch determines aging or longevity in animals

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When does aging really begin? Two Northwestern University scientists now have a molecular clue. In a study of the transparent roundworm *C. elegans*, they found that adult cells abruptly begin their downhill slide when an animal reaches reproductive maturity.

A genetic switch starts the aging process by turning off cell stress responses that protect the cell by keeping important proteins folded and functional. The switch is thrown by germline stem cells in early adulthood, after the animal starts to reproduce, ensuring its line will live on.

While the studies were conducted in worms, the findings have implications for humans, the researchers report. The genetic switch and other components identified by the scientists as playing a role in aging are conserved in all animals, including humans, offering targets for future study. (*C. elegans* has a biochemical environment similar to that of humans and is a popular research tool for the study of the biology of aging and as a model of human disease.)

Knowing more about how the quality control system works in cells could help researchers one day figure out how to provide humans with a better cellular quality of life and therefore delay degenerative diseases related to aging, such as neurodegenerative diseases.

"Wouldn't it be better for society if people could be healthy and productive for a longer period during their lifetime?" said Richard I.

Morimoto, the senior author of the study. "I am very interested in keeping the quality control systems optimal as long as we can, and now we have a target. Our findings suggest there should be a way to turn this genetic switch back on and protect our aging cells by increasing their ability to resist stress."

Morimoto is the Bill and Gayle Cook Professor of Molecular Biosciences and director of the Rice Institute for Biomedical Research in Northwestern's Weinberg College of Arts and Sciences.

The study, built on a decade of research, will be published in the July 23 issue of the journal *Molecular Cell*. Johnathan Labbadia, a postdoctoral fellow in Morimoto's lab, is the first author of the paper.

In *C. elegans*, the decline begins eight hours into adulthood—all the switches get thrown to shut off an animal's cell stress protective mechanisms. Morimoto and Labbadia found it is the germline stem cells responsible for making eggs and sperm that control the switch.

In animals, including *C. elegans* and humans, the heat shock response is essential for proper protein folding and cellular health. Aging is associated with a decline in quality control, so Morimoto and Labbadia looked specifically at the heat shock response in the life of *C. elegans*.

"We saw a dramatic collapse of the protective heat shock response beginning in early adulthood," Morimoto said.

Morimoto and Labbadia found the genetic switch occurs between two major tissues in an organism that determine the future of the species: the germline and the soma (the body tissues of the animal, such as muscle cells and neurons). Once the germline has completed its job and produced eggs and sperm—necessary for the next generation of animals—it sends a signal to cell tissues to turn off protective mechanisms, starting the decline of the adult animal.

"*C. elegans* has told us that aging is not a continuum of various events, which a lot of people thought it was," Morimoto said.

"In a system where we can actually do the experiments, we discover a switch that is very precise for aging," he said. "All these stress pathways that insure robustness of tissue function are essential for life, so it was unexpected that a genetic switch is literally thrown eight hours into adulthood, leading to the simultaneous repression of the heat shock response and other cell stress responses."

Using a combination of genetic and biochemical approaches, Morimoto and Labbadia found the protective heat shock response declines steeply over a four-hour period in early adulthood, precisely at the onset of reproductive maturity. The animals still appear normal in behavior, but the scientists can see molecular changes and the decline of protein quality control.

In one experiment, the researchers blocked the germline from sending the signal to turn off cellular quality control. They found the somatic tissues remained robust and stress resistant in the adult animals.

"This was fascinating to see," Morimoto said. "We had, in a sense, a super stress-resistant animal that is robust against all kinds of cellular stress and protein damage. This genetic switch gives us a target for future research."

The title of the paper is "Repression of the Heat Shock Response Is a Programmed Event at the Onset of Reproduction."

Provided by Northwestern University