Worm study sheds light on human aging, inherited diseases

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Microscopic worms used for scientific research are living longer despite cellular defects, a discovery that is shedding light on how the human body ages and how doctors could one day limit or reverse genetic mutations that cause inherited diseases, according to a new University of Colorado at Boulder study.

In the first formal study of its kind, researchers manipulated the metabolic state of genetically engineered lab worms called C. elegans and discovered a window of high-efficiency cellular processing that enabled the worms to slow their rate of aging. The findings could one day contribute to the creation of gene therapies to reverse or lessen the effects of mitochondrial diseases, the largest family of human genetic diseases, said lead study author Shane Rea of CU-Boulder's Institute for Behavioral Genetics.

Diseases labeled as mitochondrial are those that affect the mitochondria, the membrane-enclosed power sources present in all cells, Rea said. Researchers believe their insights might find application in treating diseases linked to mitochondrial dysfunction such as Huntington's, Parkinson's and Alzheimer's.

"We appear to have found a window where life is able to preserve itself even better than when operating in the absence of any cellular defects," said Rea. "It's a metabolic state where cells are probably getting close to the best they can be for long life and good health."

Pioneering CU-Boulder worm researcher and Professor Thomas E. Johnson and the University of Rome's Natascia Ventura co-authored the study. Grants from the National Institutes of Health and other agencies funded the research. The findings will appear in the Oct. 2 edition of the Public Library of Science journal *PLoS Biology*.

Rea, who will continue his research at the University of Texas Health Science Center in San Antonio later this year, said the study validates the worm model for research into the causes of human aging and disease.

For nearly a decade, scientists have experimented with RNA interference, or RNAi, technology to reduce gene expression with an eye toward learning more about human disease, Rea said. The technique is an effective way to silence specific pieces of DNA -- the genetic material that makes up the basic building blocks of life -- in living organisms, he said.

Rea and his team used RNAi to produce worms with varying levels of mitochondrial dysfunction with the hope of solving a mystery that has baffled scientists for years. They wanted to know why the genetically engineered worms, known as "Mit mutants," lived longer despite cellular defects that would have caused similarly damaged human cells to become diseased or die off in the lab.

The team concluded that long life occurs in worms only when energy production by their mitochondria is reduced to very discrete levels. "By tweaking cells into that tight little window of high efficiency, we may be able to increase the life span and health span of both sick and healthy people," Rea said.

The research suggests that the worms' cells receive signals from their nuclei as DNA problems are sensed and not, as previously thought, from their disrupted mitochondrial power sources. The signal-sending nuclei

order cells to shut down DNA replication, allowing them time to fix problems and create an environment that copes better with DNA damage and stress, researchers believe.

"It is only in this window that survival is enhanced. Once you move too far outside, then, like human cells, worm cells also die," Rea said. "We think there's a whole shift in the metabolism and the way it protects DNA. We show very clearly in our work that long life is intimately linked with the control of cell division."

The process appears to mimic the "hunker down" survival mode that stressed animals adopt during times of famine and danger. When conditions improve, the animals procreate again to ensure the survival of their species.

In the future, Rea and his collaborators hope to build on these findings with biochemistry and genetics to discover what controls this pro-longevity mode and how humans can reduce oxidative stress that causes cellular damage. "Life extension in humans is around the corner. There is no doubt about it," Rea said.

Source: University of Colorado at Boulder