NEW EXPERIMENT IN WORMS SLOWED AGING, PROMOTED LONGEVITY

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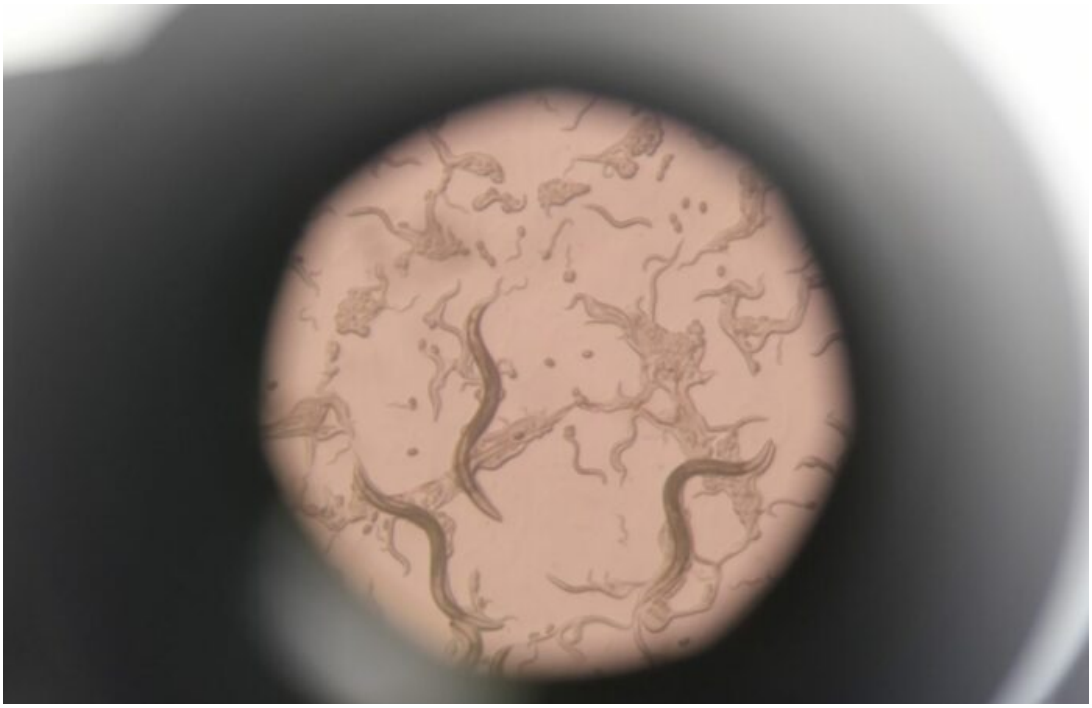

New Experiment In Worms Slowed Aging, Promoted Longevity

Researchers at Nanyang Technological University in Singapore (NTU Singapore) have discovered that 'switching on' the stress response in cells at a post-reproductive age may be the secret to delaying aging and extending life.

The NTU Singapore team conducted lab tests on a species of roundworm that is comparable to people and discovered that feeding old worms a high-glucose diet prolonged their lifetime in comparison to worms fed a normal diet by turning on this stress response in these worms.

The NTU team said that their findings, which were published today in Nature Communications, are the first to show a link between this stress response and getting older.

Although further research is required to fully understand the connection, the researchers believe their work paves the way for treatments that may prevent or slow the onset of age-related diseases like cancer, dementia, and stroke.

Associate Professor Guillaume Thibault, a cell biologist from the NTU School of Biological Sciences and the study's principal investigator, stated: "Aging is a

significant risk factor for a number of human disorders, from metabolic diseases like diabetes to cancer and neurological diseases. Finding the molecular mechanisms behind aging could advance the development of new treatment approaches to treat age-related diseases from the point of view of public health.

Although this study showed that a high-glucose diet could be beneficial to delay aging and increase longevity in old worms, “we are not recommending that the aged population should now turn to a high-sugar diet”. This work provides evidence that stimulating specific stress responses in cells may lead to increased lifespan, and that doing so using a drug may be essential for slowing the aging process within individual cells.

The NTU researchers not only demonstrated the effects of modifying this stress response in older worms, but they also demonstrated how turning off the same response in young worms fed a high-glucose diet enabled them to survive longer than worms on a regular diet.

“Metabolic diseases have serious consequences in the elderly if left untreated. This work,” according to Professor Rong Li, Director of the Mechanobiology Institute at the National University of Singapore, “is impactful because the scientists identified a cellular pathway, called the unfolded protein response, which affects lifespan in animals fed a high glucose diet.

“They found that inhibiting this pathway dramatically extended the lifespan of these animals. They therefore propose that targeting this pathway may extend lifespan in humans with metabolic disorder.”

How the stress response is triggered in cells

When stressors (such an abundance of glucose) result in a build-up of harmful “unfolded” proteins in the cell, the cell responds by producing a stress response. The unfolded protein response, or stress response, attempts to eliminate these troublesome proteins and reestablish cellular equilibrium.

Due to a natural loss in the capacity of the cell’s machinery to create healthy proteins, aging may also result in a buildup of unfolded proteins, which would cause the similar stress response.

Through its “stress sensors,” the cell’s molecular machinery combats this build-up by triggering a number of molecular reactions that will protect the cell from the stress. If the problem of too many unfolded proteins isn’t fixed, the long-term unfolded protein response kills the cell.

Unfolded protein response in elderly worms slowed aging.

The scientists used glucose to induce the unfolded protein response in adult roundworms (Caenorhabditis elegans) in order to study how this response impacts animal longevity. Although C. elegans has a far simpler physical structure than a human, it uses many of the same genes to regulate cell division and instruct defective cells to die.

Scientists gave some of the worms a high-glucose diet at two different times in their lives: when they were young (Day 1) and when they were old and no longer able to reproduce (Day 5). All the while, a control group of worms had a regular diet.

Results showed that old worms fed a high-glucose diet lasted for 24 days, about double the lifespan of young worms fed the same diet (13 days). Worms that ate normally lived for about 20 days.

Compared to worms fed a normal diet, the older worms on a high-glucose diet were more agile and had more energy storage cells, suggesting healthier aging. They also lived longer.

Long-term stress kills immature worm cells.

The NTU researchers observed the activity of the three stress sensors, each of which controls a distinct cellular pathway in the unfolded protein response, a day after giving the worms a high-glucose diet.

One of the stress sensors, IRE1, was discovered to be substantially more active in young worms than in older worms.

When scientists took out the worms' IRE1 gene to "turn off" the cellular pathway that the stress sensor starts, they discovered that the young worms fed a high-glucose diet from day one lived for 25 days, which is twice as long as when the IRE1 gene was still there.

This suggests that the longer unfolded protein response caused by the increased activity of the stress sensor IRE1 in young worms fed a high-glucose diet from day one was the cause of their shorter lives.

"We believe," as explained by Assoc Prof Thibault, "that the high-glucose diet fed to the aged worms stimulated their otherwise sluggish unfolded protein response and switched on certain cellular pathways, tackling not just the stress caused by excess glucose but also other ageing-related stress, restoring cellular stability.

"In contrast, young worms subjected to a high-glucose diet provoked unresolved stress in the cells due to an overactivated IRE1. This prolonged activation led the cells to initiate cell death instead."

He noted that the data suggest that a medication that inhibits the activity of IRE1 while raising the activity of the other two stress sensors could be produced to slow cellular aging and hence increase lifespans.

To further analyze the intricate mechanism behind the lifetime extension induced by a high-glucose diet, as well as how this mechanism interacts with other cellular processes, additional research and observations must be undertaken on roundworms.

Image Credit: NTU Singapore

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