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# Research reveals a method to slow down ageing

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

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**R**esearchers at Nanyang Technological University in Singapore (/news?tag=Singapore) (NTU Singapore) have discovered that 'turning on' the stress response in cells at a post-reproductive age may be the secret to delaying ageing and extending life. The NTU Singapore (/news?tag=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.



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The NTU team reported its findings, which were published on October 19 in Nature Communications as the first time a connection between this stress response and ageing had been discovered. The findings open the door to the creation of medicines that could delay the onset or even combat age-related illnesses like cancer, dementia, and stroke, however further research is required to fully grasp this connection.

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 ageing could advance the development of new treatment approaches to treat age-related diseases from the point of view of public health. "While our study found that a high-glucose diet could be useful to slow down ageing and promote longevity in aged worms, we are not recommending that the aged population should now turn to a high-sugar diet. What this study does show is that triggering certain stress responses in cells may translate to longevity, and that activating this stress response with a drug might be critical to decelerate cellular ageing."

Aside from showing that the effect of manipulating this stress response in aged worms, the NTU scientists also showed that the same response, when 'switched off' in young worms fed a high-glucose diet, helped them to live longer than worms on a normal diet. Commenting as an independent expert, Professor Rong Li, Director of the Mechanobiology Institute at the National University of Singapore said: "Metabolic diseases have serious consequences in the elderly if left untreated. This work 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."

This study is aligned with the research pillar of the University's NTU2025 five-year strategic plan, which focuses on health and society as one area with potential for significant intellectual and societal impact. How the cell's stress response is activated

Cells produce a stress response when stressors (such as an excess of glucose) cause a build-up of problematic 'unfolded' proteins in the cell. The stress response, called the unfolded protein response, works to clear up these problematic proteins to restore balance in the cell. Ageing could also lead to an accumulation of unfolded proteins due to a natural decline in the ability of the cell's machinery to produce healthy proteins, triggering the same stress response.

The molecular machinery in the cell tackles this build-up through its 'stress sensors', which initiate a series of molecular mechanisms to rescue the cell from this stress. If the overload of unfolded proteins is not resolved, the prolonged unfolded protein response induces cell death instead.

## Unfolded protein response in aged worms led to healthier ageing



To investigate how the unfolded protein response affects longevity in animals, the scientists induced this response in adult roundworms (*Caenorhabditis elegans*) using glucose. While *C. elegans* is significantly anatomically simpler than a human, it relies on many of the same genes that humans do to control the division of cells and to program a few cells to die. The scientists fed some of the worms a high-glucose diet at the first stage of their life cycle (Day 1), and at a post-reproductive age (Day 5), when the worms are aged and no longer fertile. A control group of worms were fed a normal diet throughout.

The scientists found that the aged worms given a high-glucose diet lived for 24 days -- almost twice the lifespan of the young worms given the same diet (13 days). Worms on a normal diet lived for 20 days. Aside from living longer, the aged worms on a high-glucose diet were more agile and had more energy storage cells as compared to worms given a normal diet, suggesting healthier ageing.

Prolonged stress response in young worms led to cell death A day after feeding the worms a high-glucose diet, the NTU scientists monitored the activity of the three stress sensors that are each responsible for a cellular pathway in the unfolded protein response.

They found that that one of the stress sensors, IRE1, was significantly more active in young worms compared to aged worms. When the scientists removed the gene coding for IRE1 in worms to 'switch off' the cellular pathway the stress sensor initiates, they found that young worms fed a high-glucose diet from Day 1 lived for 25 days -- twice as long as when the IRE1 gene was intact.

This suggests that the increased activity of stress sensor IRE1 seen in young worms fed a high-glucose diet from Day 1 -- what the scientists say is a prolonged unfolded protein response -- was responsible for shortening their lifespan. Assoc Prof Thibault said: "We believe 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." The findings suggest that a drug that reduces the activity of IRE1 while increasing the activity of the other two stress sensors could potentially be developed to decelerate cellular ageing and consequently extend lifespans, he added. (ANI)

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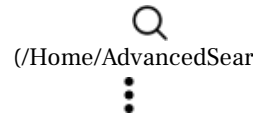
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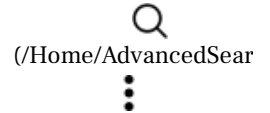
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