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Protecting cells: Evidence found for a neuronal switch to prevent neurodegenerative diseases

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Scientists at Northwestern University report a surprising discovery that offers a possible new route for the treatment of neurodegenerative diseases. In a study of the transparent roundworm *C. elegans*, they found that a genetic switch in master neurons inhibits the proper functioning of protective cell stress responses, leading to the accumulation of misfolded and damaged proteins.

Neurodegenerative diseases, ranging from Huntington's and Parkinson's to amyotrophic lateral sclerosis and Alzheimer's, are believed to stem from early events that lead to an accumulation of damaged proteins in cells. Yet all animals, including humans, have an ancient and very powerful mechanism for detecting and responding to such damage, known as the heat shock response.

"Why are these diseases so widespread if our cells have ways to detect and prevent damaged proteins from accumulating?" said Richard I. Morimoto, who led the research together with postdoctoral colleague Veena Prahlad. "Can our body fix the problem? That is the conundrum."

"In our study, much to our surprise, we discovered that the nervous system sends negative signals to other tissues in the animal that inhibit the ability of cells to activate a protective heat shock response," Morimoto said. "The machinery to repair the damaged proteins is intact, but the nervous system is sending a signal that prevents it from doing its

job."

When the signal from the nervous system was reduced, the cells' heat shock response returned, leading to elevated levels of special protective proteins, called molecular chaperones, that kept the damaged proteins in check.

Morimoto is the Bill and Gayle Cook Professor of Biology in the department of molecular biosciences and the Rice Institute for Biomedical Research in Northwestern's Weinberg College of Arts and Sciences.

The findings are published by the Proceedings of the National Academy of Sciences (*PNAS*).

"Currently, we have no solution for these devastating diseases," Morimoto said. "This master neuronal switch could offer a new target for therapy. If we can restore the natural ability of cells to prevent protein damage, our cells should be healthier longer and the quality of life will be better."

The findings are also applicable to other diseases that involve protein misfolding, such as cancer and metabolic diseases, Morimoto said.

Morimoto and Prahlad studied *C. elegans*, specifically models with different forms of protein misfolding diseases. The transparent roundworm is a valued research tool as its biochemical environment is similar to that of human beings and its genome, or complete genetic sequence, is known.

They interfered with the nervous system signal, the "master switch," to see what would happen to the animals. When the signal was working, the animals accumulated damaged proteins in their cells that interfered with

cellular function. But when the researchers reduced the neuronal signal a little bit, the normal cellular response to protein damage returned and the animals were healthy.

While the downregulation of the neuronal signal in the study was done genetically, in humans the idea would be to alter the signal chemically, Morimoto said.

"This work gives us an appreciation that animals are not just a bundle of cells, each on its own to sense and respond to damage," he said. "The cells are organized into tissues, tied into a network that is organized by the brain. The brain can tell the cells to turn on a stress response or not. The nervous system is talking to all the parts to orchestrate an organismal response to stress. That's what's so fascinating."

More information: The paper, titled "Neuronal circuitry regulates Q:1 the response of Caenorhabditis elegans to misfolded proteins," is available at www.pnas.org/content/early/201 … /1106557108.abstract

Provided by Northwestern University

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