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Even when you're older you need chaperones

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Aging is the most significant and universal risk factor for developing neurodegenerative diseases, such as amyotrophic lateral sclerosis (ALS) and Alzheimer's, Parkinson's and Huntington's diseases. This risk increases disproportionately with age, but no one really knows why.

Now a team of scientists from Northwestern University, Proteostasis Therapeutics, Inc. and Harvard University has uncovered some clues. The researchers are the first to find that the quality of protective genes called molecular chaperones declines dramatically in the brains of older humans, both healthy and not, and that the decline is accelerated even more in humans with neurodegenerative disease.

Molecular chaperones are a special set of highly conserved genes that watch over cells, keeping them and the entire organism healthy by preventing protein damage.

The researchers specifically found the decline in 100 genes, approximately one-third of all human molecular chaperone genes. Then, with additional studies, they winnowed that number down to 28 human genes specifically involved in age-associated neurodegeneration. These critical genes provide a basis for a biomarker, an early indicator of disease and a target for new therapeutics.

"Imagine if we had biomarkers that tell doctors how you are doing in terms of aging, warning of any problems long before neurological deficits appear," said Northwestern's Richard I. Morimoto, one of the senior scientists on the study. "This would be a remarkable tool,

especially considering the increases in life expectancy in many parts of the world.

"Let's say a person is age 50, but we see his molecular chaperones have declined and aren't repairing proteins and cellular damage. The chaperones are acting more like age 85 or 90. That's a sign that medical intervention could help," he said.

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

"Molecular chaperones really are the barrier we have between disease and no disease," Morimoto said. "If this critical system declines, it leads to misfolded and damaged proteins, and eventually tissues become dysfunctional and die. If we can keep the chaperones healthy, we should be able to keep the person healthy."

The study will be published in the Nov. 6 issue of the journal *Cell Reports*.

To zero in on the subnetwork of 28 key genes, the scientists combined genomic analysis of human brain tissue, from both healthy individuals and those with neurodegenerative diseases (Alzheimer's, Parkinson's and Huntington's), with functional studies of C. elegans, a transparent roundworm. (The worm has a biochemical environment similar to that of human beings and is a popular research tool for the study of human disease.)

"To our surprise, the results from the studies of humans and C. elegans told us the same thing—10 percent of the 332 human genes are really important to cell health," Morimoto said. "Now we are down to 28

genes. This really tells us what to focus on."

After observing the dramatic decline in the health of molecular chaperones in humans both healthy and with neurodegenerative disease, the researchers systematically and individually "knocked down" all 219 chaperone genes in C. elegans (using neurodegenerative disease models) to see what effect the gene's absence had on an animal's function.

They identified a subnetwork of 16 molecular chaperone genes in C. elegans that are critical to preventing protein misfolding and damage to the cell. These genes correspond to 28 human "cousin" genes.

Humans encode approximately 25,000 genes, and getting any process down to a small number of genes will help scientists put their fingers on what's most important.

"It's a lot easier to enhance a handful of genes, such as those we've identified," Morimoto said. "The next step is to understand the basis for the decline of these specific chaperones and to develop treatments that prevent their decline. The goal is not to make people live forever but rather to match health span more closely with life span—to improve the quality of life being lived."

More information: The title of the paper is "A Chaperome Subnetwork Safeguards Proteostasis in Aging and Neurodegenerative Disease."

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