Misfolded proteins: The fundamental problem is aging

August 24 2009

Proteins are essential for all biological activities and the health of the cell. Misfolded and damaged proteins spell trouble and are common to all human neurodegenerative diseases and many other age-associated diseases. But when during a lifespan do proteins start to misbehave?

A new Northwestern University study reports that protein damage can be detected much earlier than we had thought, long before individuals exhibit symptoms. But the study also suggests if we intervene early enough, the damage could be delayed.

In studying seven different proteins of the worm *C. elegans*, the researchers discovered that each protein misfolds at the same point: during early adulthood and long before the animal shows any behavioral, or physiological, change. (Each protein had a minor mutation that affects folding.)

The misfolding coincided with the loss of a critical protective cellular mechanism: the ability to activate the heat shock response, an ancient genetic switch that senses damaged proteins and protects cells by preventing protein misfolding.

The results will be published online during the week of Aug. 24 by the Proceedings of the National Academy of Sciences (*PNAS*).

"I didn't expect the results to be so dramatic, for these different proteins that vary in concentration and are expressed in diverse tissues to collapse

at the same time," said lead researcher Richard I. Morimoto. "This suggests the animal's protective cellular stress response becomes deficient during aging."

Could the damaging events of protein misfolding be prevented or at least delayed?

To find out, the researchers gave the animals the equivalent of a vitamin, boosting the heat shock response early in the animal's development, prior to protein damage. Now, instead of misfolding around day four, the equivalent of early adulthood in the worm, the proteins didn't start misfolding until day 12. (Behavioral changes didn't appear for at least three days after misfolding. The average lifespan of the worm is 21 days.)

"Our data suggest that, in terms of therapeutics, you have to start early to prevent damage and keep cells healthy," said Morimoto, Bill and Gayle Cook Professor of Biochemistry, Molecular Biology and Cell Biology in Northwestern's Weinberg College of Arts and Sciences. "When you see a loss of function, it's too late."

Genes that regulate lifespan were first discovered in *C. elegans*. The transparent roundworm is a favorite organism of biologists because its biochemical environment and fundamental mechanisms are similar to that of human beings and its genome, or complete genetic sequence, is known.

More information: The title of the *PNAS* paper is "Collapse of Proteostasis Represents an Early Molecular Event in C. elegans Aging." In addition to Morimoto, other authors of the paper are Anat Ben-Zvi and Elizabeth A. Miller, both from Northwestern.

Source: Northwestern University (news : web)