Scientists solve long-standing mystery of protein 'quality control' mechanism

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Scientists from The Scripps Research Institute have solved a long-standing mystery of how cells conduct "quality control" to eliminate the toxic effects of a certain kind of error in protein production. The findings may lead to a better understanding of a host of neurodegenerative diseases.

The research was published in an advance, online issue of the journal *Nature* on September 12, 2010.

"It is exciting because we are dealing not only with a process that is clearly relevant for physiology and disease," said Scripps Research Assistant Professor Claudio Joazeiro, who led the study, "but also with new biology."

The new study suggests how cells in eukaryotic organisms, like humans, sense and destroy "non-stop" proteins that remain stuck in the ribosome, the protein manufacturing plant of the cell.

Proteins "R" Us

It's hard to overemphasize the importance of proteins in the body, as they participate in virtually every cellular process. Proteins are the end result of one of the central tenets of biology (known as the "central dogma"), which tells us that DNA is used to make RNA, which, in turn, is used to make proteins. In healthy cells, the ribosome translates the

code carried by a messenger RNA (mRNA) to link together protein building blocks (amino acids) in a particular order to form specific proteins.

But errors happen—which is why the body has a host of different quality control mechanisms to ensure that the proteins that emerge from this process are flawless. When aberrant proteins escape these surveillance mechanisms, they accumulate and form "aggregates" that can be toxic to certain neuronal types, and disorders such as Alzheimer's and Parkinson's diseases can result.

One element in mRNA essential to this protein manufacturing process is known as a "stop codon." A stop codon both signals the end of the mRNA coding sequence to the ribosome so it stops assembling the protein, and recruits factors that promote the protein's release into the cellular cytoplasm so the protein can go forth and perform its biological functions. When mRNA is accidentally missing a stop codon, however, the ribosome is like an auto manufacturing plant that can't get a car off the end of the line—the line stalls and production stops.

"In addition, these defective mRNA are problematic because they are translated into aberrant proteins," explained Joazeiro. "For these reasons, there are machineries in all living organisms—whether bacteria or more complex eukaryotic organisms—that target and destroy both these non-stop messenger RNA and the resulting non-stop proteins."

For some 15 years, scientists have understood the mechanism that identifies and destroys these problematic non-stop proteins in bacteria. In these organisms, non-stop proteins are tagged by a marker known as tmRNA or ssrA, which then leads to their destruction.

In more complex eukaryotic organisms, which range from yeast to humans, though, the mechanism for identifying and eliminating such

dangerous non-stop errors has remained a mystery—until now.

A Fresh Approach

Previously, scientists had failed to discover the missing quality control mechanism using a "homology" approach, in which they searched for molecules from eukaryotic organisms that looked like the bacterial tmRNA. Joazeiro and a postdoctoral fellow in his lab Mario Bengtson got to the mechanism by a different path.

In collaboration with Steve Kay's lab (now at the University of California, San Diego) the Joazeiro lab had discovered that a strain of mice carrying a mutation in a molecule known as Listerin experienced neurodegeneration. Because of recent studies from other labs and their own, the scientists suspected that Listerin could have a role in non-stop protein degradation.

To investigate, in the current study Joazeiro and Bengtson used the yeast S. cerevisiae as a model organism. Yeast is complex enough to share many cellular features with other eukaryotes such as mice and humans, yet relatively simple to work with in the lab. Most importantly, since it possesses a short lifecycle, yeast experiments can yield results more quickly.

When the results were in, they showed that cells without Listerin (called Ltn1 in yeast) failed to get rid of non-stop proteins and died when those proteins were produced. Ltn1 was the long-sought missing link for non-stop protein degradation—even though it looked nothing like tmRNA/ssrA.

In addition to revealing Ltn1's function, in the study the scientists went on to describe the mechanism by which it worked. Joazeiro and Bengtson found that Ltn1 binds to ribosomes and tags nascent non-stop

proteins with ubiquitin molecules—a common signal for protein destruction in cells of eukaryotic organisms.

"The [bacterial and eukaryotic] mechanisms are very different, but the concepts are remarkably similar—that's the beauty of it," said Joazeiro. "It also turns out that in the same way that the tmRNA molecule is conserved in all bacteria, Listerin is conserved in all eukaryotes, which once again highlights its importance. It appears that between tmRNA and Listerin we have coverage throughout most living organisms of the surveillance of these defective proteins."

While the study solves a fundamental biological mystery, many questions remain. To what extent is this process similar in mice or humans? Would a defect in Listerin's role in protein quality control account for the neurodegeneration in the mutant mice? Are there human neurodegenerative diseases caused by Listerin mutation? The Joazeiro lab continues to investigate.

More information: Research paper is titled "Role of a ribosome-associated E3 ubiquitin ligase in protein quality control".

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