

JUNE 24, 2004

Researchers Discover a Channel for Protein Waste

Researchers have discovered a type of channel within cells that is responsible for funneling misfolded proteins and other cellular garbage to the appropriate waste disposal site within the cell.

The discovery of the channel-like protein Derlin-1 represents a milestone for researchers who have been working for many years to uncover key proteins involved in the disposal of malfunctioning proteins. Derlin-1 is also a target for hijacking of the cellular waste-disposal machinery by cytomegalovirus, a virus that is estimated by the Centers for Disease Control and Prevention to infect 50-85 percent of adults in the United States by the age of 40. The virus protects itself from attack by the immune system by deceiving the disposal system into mistaking important immune defense proteins for garbage to be discarded.

The researchers said that additional insight into the machinery for transporting misfolded proteins could offer improved understanding of a range of inherited diseases, including cystic fibrosis, in which misfolded proteins are degraded before they can assume their normal function.

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- **Tom A. Rapoport**

The new insights into the protein-disposal machinery were reported in two papers published in the June 24, 2004, issue of the journal *Nature*. Howard Hughes Medical Institute investigator [Tom A. Rapoport](#) at Harvard Medical School led one research group; Hidde L. Ploegh, who is also at Harvard, led the second group

Both groups were exploring the machinery underlying a phenomenon known as retrotranslocation in the endoplasmic reticulum (ER) of the cell. The ER is a highly convoluted membrane within the cell to which proteins are “translocated” after being synthesized in the cell's cytosol. Once in the ER, the proteins are folded into functional shapes and marked for transport to various destinations within the cell.

It turns out, however, that the cell uses retrotranslocation to deal with misfolded proteins, which must be destroyed before they gum up the cell. “People initially thought that misfolded proteins in the ER were degraded inside the ER,” said Rapoport. “So, it was a big surprise when it was discovered only about ten years ago that most such proteins are transported back into the cytosol and degraded there by the machinery of the proteasome. Thus, rather than inventing another degradation system inside the ER, the cell is using the same machinery,” he said.

So far, though, the machinery that the cell uses to transport misfolded proteins across the ER membrane to be degraded has remained largely mysterious. In their *Nature* article, Ploegh and his colleagues describe the approach they used to identify Derlin-1 as a major component of retrotranslocation. To pinpoint Derlin-1, the researchers tagged a protein, called US11, which cytomegalovirus uses to divert immune system proteins to be retrotranslocated from the ER. Their tracking of how the tagged viral protein binds to the retro-translocation machinery revealed the presence of the previously unknown Derlin-1—a mammalian counterpart of a similar protein in yeast.

Rapoport and his colleagues took an alternate approach that led to their discovery of Derlin-1, which they describe in their *Nature* article. Previous work by the article's lead author, Yihong Ye, had revealed that an enzyme called p97 is part of the machinery in the cytosol that “pulls” the protein to be degraded from the ER membrane. Reasoning that p97 quite likely interacts with a receptor in the ER membrane, the researchers used p97 as a sort of molecular fishhook to isolate the receptor protein—which turned out to be Derlin-1. In the process, the researchers also discovered a second component of the retrotranslocation machinery, which they named VIMP.

In further experiments, the researchers established that Derlin-1 and VIMP are both involved in the viral hijacking of the retrotranslocation machinery by the protein US11.

Co-authors Chi Yun and David Ron of New York University School of Medicine conducted studies using the roundworm *C. elegans* to explore the consequences of blocking the expression of Derlin-1. They found that blocking Derlin-1 induces a form of cellular stress that occurs when misfolded proteins accumulate in the ER. These findings provided further evidence that Derlin-1 is a central component of retrotranslocation.

The researchers have formulated a model of how the retrotranslocation machinery works. They suggest that the machinery is triggered when either the viral protein US11—or a similar cellular molecule that recognizes misfolded proteins—targets a protein for retrotranslocation, said Rapoport.

“We think that Derlin-1 forms a channel in the ER membrane and that it associates with the VIMP protein, which extends into the cytosol. The VIMP then recruits p97, which we have good reason to believe pulls the protein into the cytosol so that it can be delivered to the proteasome for degradation.”

Future studies in Rapoport's laboratory will concentrate on identifying the cellular proteins that are the counterparts of the viral protein US11. Also, the researchers will be trying to identify the interaction partner of p97 in yeast, where VIMP does not exist.