Quality-control mechanism found in bacteria

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(Phys.org) -- Like quality-control managers in factories, bacteria possess built-in machinery that track the shape and quality of proteins trying to pass through their cytoplasmic membranes, Cornell biomolecular engineers have shown.

This quality-control mechanism is found in the machinery of the twin-arginine translocation (TAT) pathway, which is a protein export pathway in plants, bacteria and archaea (single-celled microorganisms). The transport of proteins across cellular membranes is a basic life process and understanding how the TAT pathway works could lend insight into, for example, how bacteria become resistant to antibiotics.

The discovery is a milestone in a 10-plus year study of the TAT pathway led by Matthew DeLisa, associate professor of chemical and biomolecular engineering, and is detailed in Proceedings of the National Academy of Sciences, July 30.

"Our first paper on this topic [PNAS, May 13, 2003] suggested that, given the fact that only folded proteins can go through this system, perhaps a quality-control mechanism was embedded in the machinery itself," DeLisa said. "That idea turned out to be controversial, but this most recent paper, we think, reopens that possibility.

"There are no other mechanisms that we're aware of where the transport machinery itself participates directly in the quality control of its substrates. The discovery [of our research] is … paradigm shifting as far as biological transport machinery goes," DeLisa said.

The TAT pathway is remarkable because, unlike other similar processes, the protein cargo passes through the cell membrane in tightly folded shapes, as opposed to long strings. The pathway allows properly folded proteins to pass, while badly folded or damaged ones are not permitted through.

DeLisa and colleagues Mark Rocco, a graduate student, and Dujduan Waraho-Zhmayev, a postdoctoral associate, used an old trick to make this new discovery: They set up a genetic selection experiment that enables researchers to link genetic mutations to the survival of a cell carrying that mutation.

Using a genetic selection for TAT export, they were able to isolate a mutation known as a suppressor in the TAT machinery that allowed the bacteria to survive if they exported misfolded proteins. They concluded that the bacteria's survival was attributed to their ability to export misfolded proteins, which normal bacteria in nature wouldn't do. The team's findings provide the first direct evidence for the participation of the TAT machinery in regulating the export of proteins.

The TAT machinery, they speculate, contains a component that senses whether a protein is folded properly and discriminates between folded or unfolded proteins, allowing export of only the well-folded ones.

The new insight into how the TAT pathway regulates the quality of proteins adds to a growing base of science underlying Ithaca biotechnology company Vybion's proprietary antibody development technology called ProCode.

Several years ago, DeLisa's initial research on the TAT pathway formed the basis of several inventions that have been licensed by Vybion, which is using the technology for creating new antibody drugs, particularly for such diseases as Alzheimer's.

"All of these mechanisms, including the quality control feature, together are elements of the ProCode technology and should be useful in the hunt for 'good' antibodies that bind specifically to their target and are very well behaved from a folding standpoint," said DeLisa, who serves on Vybion's advisory board.

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