Mutant prions help cells foil harmful protein misfolding

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Romping clumps of misfolded proteins are prime suspects in many neurological disorders including Alzheimer's, Parkinson's, and Creutzfeld-Jakob Disease. Those diseases are devastating and incurable, but a team of biologists at Brown University reports that cells can fix the problems themselves with only a little bit of help. The insight suggests that there are more opportunities to develop a therapy for protein misfolding than scientists had thought.

"There are multiple steps that you could target," said Susanne DiSalvo, a Brown biology graduate student and lead author of a paper published in advance online March 20 in Nature Structural and Molecular Biology.

In the study, the research team, led by Tricia Serio, associate professor of medical science, explains how two different beneficial mutant prions managed to foil the amplification of harmful clumps of misfolded proteins in yeast. Cells have an internal quality assurance system to break up and refold misfolded proteins, but that system can be overwhelmed by diseases. DiSalvo was the first to observe that the mutants act at distinct stages to tip the balance back in favor of the cells, allowing them to overcome the problem.

Serio says the molecular mechanisms appear to explain how similar mutants solve protein misfolding in mammals, including people. The phenomenon had been poorly understood and has never been exploited to develop a successful therapy.

Misfolding is a vulnerable process

Until now most scientists guessed that the only way to stop the runaway misfolding was right at the beginning and assumed the mutants must be blocking that first step to keep the protein in a harmless form. DiSalvo's work instead suggests that there are many opportunities throughout the process where even a mild intervention could give cells what they need to gain the upper hand, Serio said.

"That's one of the biggest outcomes of Susanne's work: that if you just even slightly interfere with this process, the cell can deal with it and get rid of it," Serio said. "The dogma in the field is that these conformations were so abnormal the cell couldn't resolve them. But what we've found is that this process of misfolding is so efficient the cells can't keep up with it. If you make it even just a little bit less efficient the cell can get rid of the pathological state."

One mutant prion, Q24R, hinders the ability of misfolded proteins to aggregate into harmful clumps. It's like a dryer sheet that cuts down on static cling and makes it easier to fold laundry. Another helpful mutant prion known as G58D, assists the cell by speeding up its ability to unfold and refold misfolded proteins. That's more like a friend who helps untangle strings of holiday lights when they come out of storage.

DiSalvo's experiments showed how the mutants and cells work together. Cells would only be cured when she both added a mutant and allowed the cells' own quality assurance system to work. Adding the mutant G58D, for example, could cure a cell of infection by the Sup35 prion, but if she perturbed the cell's quality assurance system then G58D would not work.

The results show the importance of delving deeply into molecular networks, said Stefan Maas, who oversees Serio's and other cellular signaling grants at the National Institutes of Health.

"These results are a great example of the power of system-level studies," Maas said. "By showing how two beneficial mutants cure the cell of prions, this study has revealed that small changes applied to distinct components of a molecular network can dramatically alter the outcome for the cell. These new insights may lead to new strategies for preventing or treating disorders that involve protein deposits."

But those strategies may require turning proteins into pills. Serio noted that while beneficial mutant prions confer resistance to prion infection in nature, they haven't been successful in reversing an established infection because sustained delivery into the body is too challenging. However, a small molecule drug mimic, if developed, could target infected tissues more effectively over a longer period to slow or perhaps even reverse disease progression.

In the paper the researchers conclude, "A system-based approach to prion intervention represents a potentially promising direction in which to explore future therapies."

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