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Yeast Prions Spur Generation of New Traits

Researchers have discovered that misfolded yeast prion proteins might serve a useful evolutionary purpose by spurring the generation of novel proteins that may underlie new adaptive survival traits.

The yeast prions' abnormal shape causes the protein-making machinery to ignore signals that stop protein production. These signals can be natural signals that govern protein production or those that prevent expression of genes that had previously remained "silent." Once the stop signals are bypassed, useful mutations may accumulate in yeast that allow the organism to adapt to conditions in the environment.

Prions may play a broad role in genetic diversity, say the researchers, because they may be vehicles for allowing mutations to accumulate in a harmless fashion, to be tried out later. This branch of prion research may yield clues about how evolution can abruptly give rise to complex new traits, when incremental mutations leading to those traits would be harmful.

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Howard Hughes Medical Institute investigator Susan L. Lindquist and University of Chicago colleague and lead author Heather True published their findings in the September 28, 2000, issue of the journal *Nature*.

In their studies, the researchers explored the effect of the yeast prion Sup35 on protein synthesis. Lindquist and her colleagues had previously shown that Sup35 could transmit heritable characteristics from one generation of yeast to the next, bypassing DNA- and RNA-based modes of inheritance. Yeast prions are conceptually similar to the mammalian prions notorious for their roles in the fatal brain-destroying human diseases as Creutzfeldt-Jakob disease and kuru, and in the animal diseases, scrapie and spongiform

encephalopathy, or "mad cow disease."

Both yeast and mammalian prions transmit phenotypes via protein-protein interactions, in which an abnormally shaped prion protein influences its normal counterpart to assume an abnormal shape. In mammalian prion infection, such abnormal, insoluble shapes cause protein clumping that kills brain cells. In yeast cells, however, the insoluble prion protein is not deadly, but it alters protein synthesis.

"We knew that Sup35 works by allowing the protein synthesis machinery to read through stop codons on messenger RNA at a low level," said Lindquist. "For example, experiments showed that the prions allowed read-through of laboratory-induced nonsense mutations on a gene required for growth.

"One view of this behavior has been that the prion is some weird freak of nature," she said. "But I have suspected for a long time that it might have a biologically interesting function in allowing a change in gene expression that is actually useful to yeast.

"We may not have noticed such variation in our studies initially because we hadn't been looking for their phenotypes," said Lindquist. "We had been growing the cells under laboratory conditions where they were not facing the rigors of the wild."

To test whether prions could alter normal protein expression or unveil silent genes, True and Lindquist grew matched prion-containing and non-prion-containing strains of yeast under a wide variety of conditions that they hoped would reveal the presence of prion-induced variation. They studied the responses of the yeast strains to alterations in 150 conditions, including different nutrient sources, temperatures and stress conditions, as well as the presence of antibiotics and other inhibitors of various cellular processes.

"We found that in each of the strains we tested, when it was switched to the prion state, had a different pattern of growth properties," said Lindquist. "That told us that there was hidden variation in each of these strains—a richness in growth capacity that didn't show up under normal growth conditions. This variation was triggered by prions."

According to Lindquist, the prions might create new diversity in at least two different ways. One way is that switching from a normal to a prion state might enable the yeast to ignore natural genetic stop signals that control the production of properly functioning enzymes. Ignoring stop signals might allow a protein to become slightly longer, altering its enzymatic properties in ways that might prove advantageous—for example, by increasing antibiotic resistance.

A second possible explanation is that the prion might cause yeast to ignore stop signals that prevent the translation of genes. By reawakening these normally silent genes, prions may unleash the generation of new traits in yeast.

Lindquist said that mammalian prions do not work in the same way, "but it does certainly make one think that the kinds of conformational changes that mammalian prions undergo could potentially have some beneficial effects, too."

She also emphasized that the discovery of prion-induced variations in yeast should encourage the search for other mechanisms in cells by which hidden variations can suddenly be revealed on a genome-wide scale. These might provide a route to study variations in traits that usually require multiple genetic changes. Discovering such mechanisms could help settle a long-running debate over whether evolution is always a gradual process or whether it can occur in sudden leaps, avoiding intermediate forms that might be detrimental to an organism.

"There may be many mechanisms by which organisms can store genetic variation and then suddenly reveal it," she said. "They could provide a way to facilitate the pace of evolutionary change. Or, in the case of the prion, they could allow an organism to have more than one kind of stable, heritable set of traits allowing it to adapt to a fluctuating environment without actually changing its genome."