Prions can pass on beneficial traits, study finds

October 3 2016

Prion proteins, best known as the agents of deadly brain disorders like mad cow disease, can help yeast survive hard times and pass the advantageous traits down to their offspring, according to a new study by researchers at the Stanford University School of Medicine.

The study, to be published in the Oct. 6 issue of *Cell* and already available online, indicates that in yeast—and possibly other organisms, including humans—protein-based inheritance is more widespread than previously believed, and could play a role in evolution.

"In evolution there's a paradox," said Daniel Jarosz, PhD, assistant professor of chemical and systems biology and of developmental biology, who is lead author of the study. "We know that there are an extraordinary number of mechanisms that exist to protect the integrity of the genetic code and to assure that it's faithfully passed on to future generations. But we also know that evolutionary success requires adaptability. How can you reconcile that need with the fact that the raw material for that innovation is really limited?"

Jarosz had a hunch that prions might be part of the answer. The new study suggests this could be the case.

How prions work

To understand his hunch, you need to know a bit about how prions work.

Let's consider this scenario in a bottle of beer on a hot summer day: When some of the yeast cells floating in your beer get stressed, in this case by the blazing sun, they begin producing large quantities of proteins called molecular chaperones—or proteins that help other proteins fold. These chaperones wrap around prions and fold them into a shape that kicks off a chain reaction of sorts. Other prions of its kind follow suit, using the original as a template.

"I sometimes liken it to a spreading fashion trend among teenagers," said Jarosz. "Once it catches on with a couple of kids it spreads rapidly to other teenagers. But only teenagers."

The upshot is that a single prion can quickly convert many others to assume the same shape—and since a protein's shape dictates its behavior, that means the prion converts the other proteins' behavior as well. Furthermore, when a cell divides, both new cells are likely to carry prion proteins that will continue to spur conversions. That means the offspring will also display the new behavior, a result of inheritance perpetuated not through the standard means of DNA but instead by way of proteins.

In the case of mad cow disease, a prion leads its normal brethren to fold in a way that leads to tissue damage in the brain and spinal cord of cattle. A human version of the disease, called variant Creutzfeldt-Jakob disease, can result from eating beef products from infected cattle.

They're not all bad

But Jarosz knew that not all prions are bad. He had learned about a few beneficial ones from his time as a postdoctoral scholar at the Whitehead Institute for Biomedical Research in the laboratory of Susan Lindquist, PhD, a co-author of the study who has pioneered investigations of prions as a driver of inheritance. When Jarosz came to Stanford as an assistant

professor in 2013, he began what would become a nearly three-year project to systematically assess an organism for prion-based inheritance. He chose yeast, he said, because researchers around the world have established the organism's genetics and have developed comprehensive tools to analyze them.

"I wanted to know the breadth of protein-based inheritance across the yeast genome. Is it really so rare?"

With the help of several robots, his team overexpressed nearly every yeast gene, one by one, for 48 hours—triggering each gene to create 10 to 100 times more copies than usual of the protein designated by its code. Of the 5,300 genes they revved up, they found 46 made proteins that led to traits that remained heritable many generations after their expression had returned to normal. The traits were generally beneficial, such as resistance to temperature stress and anti-fungal drugs, or enhanced growth at high temperatures.

When they analyzed the proteins' shapes, they discovered that few of them resembled what researchers had expected prions to look like. Most previously known prions fold in such a way that they pack tightly together and form long fibrils. The newly discovered prions lacked that trait, but many had others in common: They were strongly attracted to DNA molecules and they featured long, floppy "arms" able to fold in a wide variety of ways.

Non-Mendelian inheritance

Digging up unknown prions in yeast is less dangerous than you might think, said Jarosz. The efficiency of cross-species templating is very low for prion proteins. "This is probably one of the major reasons that mad cow disease wasn't more widespread," he said. "There is a safety concern with the human proteins. But luckily, simple procedures, like treating

with bleach or soaking in sodium hydroxide, can render these protein conformations harmless."

The team also found that the traits followed prionlike inheritance patterns. For example, unlike traits resulting from most genetic mutations, prion traits are dominant, and they don't obey Mendel's laws. Rather than being passed to half of all progeny in genetic crosses—as Mendel saw with his peas—prion-based traits are transmitted to every cell.

Additionally, when the researchers temporarily inhibited chaperone proteins, the prion-based traits were permanently eliminated.

For the ultimate test, the researchers destroyed the DNA in the yeast cells carrying what they believed were prion-based traits, collected the remaining cell contents and introduced it into ordinary yeast cells. They found the traits were transmitted even though the cell's DNA had been destroyed—indicating that proteins were transmitting the traits instead.

The researchers also found several human genes that would make proteins with similar characteristics. "These domains have been widely conserved across evolution, and several human homologs had the capacity to fuel protein-based inheritance," they wrote in the study. "Our data thus establish a new and common type of protein-based molecular memory through which intrinsically disordered proteins can drive the emergence of new traits and adaptive opportunities."

Provided by Stanford University Medical Center