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Researchers Show that Proteins Can Transmit Heritable Traits

In an achievement that could lead to new techniques for genetic manipulation, Howard Hughes Medical Institute (HHMI) researchers at the University of Chicago have altered a protein to transmit a specific trait from one generation of yeast cell to another.

Their latest work builds on the discovery of a protein that transmits a genetic trait, a finding that hints at the presence of a menagerie of undiscovered protein-based "genetic elements" that may have driven evolution without the need for mutation of DNA genes.

Led by HHMI investigator Susan Lindquist at the University of Chicago, the researchers reported their findings in the January 28, 2000, issue of *Science* and in the January 2000 issue of *Molecular Cell*.

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- Susan Lindquist

"Most people think of genetics as being only about DNA," said Lindquist. "But genetics is about the inheritance of traits. While most traits are inherited through transmission of DNA, the traits we study are inherited through proteins. Thus, these proteins can be every bit as much a genetic element as DNA. After all, they are heritable entities that span generations and influence a cell's phenotype in a predictable way."

In both studies, Lindquist's research team worked with yeast proteins known as "prions," which they and others had previously discovered could transmit different characteristics, called phenotypes, from one yeast generation to another.

Yeast prions are similar to mammalian prions that have gained notoriety for their roles in such fatal brain-destroying human diseases as Creutzfeldt-Jakob disease and kuru, and in the animal diseases, scrapie and bovine 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, the insoluble prion protein is not deadly; it merely alters a cell's ability to function.

In the *Science* article, Lindquist and colleague Liming Li described the startling discovery that a yeast prion called Sup35 consists of modular sections, or domains, that can be attached to other proteins to transform them into prions.

In their experiments, the scientists created a fully functional artificial prion by attaching the prion-determining domains of Sup35 to a rat protein called a glucocorticoid receptor.

"We chose the rat protein because it was quite different from anything found in yeast," said Lindquist. "And we showed that this protein that was completely foreign to yeast could, in effect, be turned into a new type of yeast genetic element."

The scientists also found that they could switch the yeast cell phenotype back and forth between the two forms by using simple biochemical manipulation.

According to Lindquist the ability to affect inheritance of phenotypes by altering proteins to transmit shape changes offers a powerful new approach to exploring cells' machinery by selectively turning off specific proteins.

"This technique offers a general mechanism for causing a dominant loss of function in cells," she said. "And it's switchable, because by simple laboratory manipulation, you can induce a cell to flip from one phenotype to another." By contrast, she said, techniques of using DNA mutation to alter such phenotypes are highly specific to each protein and cannot be reversed.

In the article published in the journal *Molecular Cell*, Lindquist and colleague Neal Sondheimer described the first discovery of a new yeast prion resulting from a deliberate search. The current known yeast prions had been found accidentally.

Lindquist and Sondheimer used a stringent set of molecular criteria in their search for candidate yeast prions, and their experiments pinpointed a likely candidate, called Rnq1.

To prove that Rnq1 was indeed a prion, they substituted the prion-like domain of Rnq1 for its counterpart in the Sup35 prion. They found that the altered Sup35 continued to behave as a prion, as did the natural Sup35 prion

protein.

"The fact that these prion domains proved so modular and transferable, as revealed in these papers, proved quite a surprise," said Lindquist. "Since prions such as Sup35 had evolved to have the same general structure for many millions of years, one might have expected their different domains to have evolved together to influence one another.

"This modularity suggests that as species evolved, other proteins might have picked up these prion domains and become genetic elements. If they did, this kind of protein inheritance pattern could have had an important effect on the process of evolution."