Yeast for Thought

First in yeast, and then in laboratory creatures with nerve cells, researchers have discovered how the Parkinson's disease process may be curtailed.

Jason Grow

Susan Lindquist called in colleagues to see if her findings in yeast would hold up in animals with neurons and brains.

YEAST MIGHT NOT BE THE MOST OBVIOUS EXPERIMENTAL MODELS FOR NEURO-degenerative diseases. For one thing, they don't have brains. ¶ But these single-celled creatures get sick and die from the same toxic culprit that mucks up dopamine-producing neurons in Parkinson's disease. Now, a multi-institutional team led by HHMI investigator Susan Lindquist has found a way to reverse the damage in yeast. Even better, the team confirmed the same defect and cure in dopamine-producing neurons of fruit flies, roundworms, and rats.

The findings reveal how simple yeast may speed up the search for new therapeutics for complex brain diseases that are hard to study in people. "We put a human gene into an organism that separated from us in evolution one billion years ago, and we found the same biochemical activity," Lindquist says. "This is a new way to understand the biology and a potential mechanism for discovering drugs."

Three years ago, researchers in Lindquist's lab at the Whitehead Institute for Biomedical Research (Cambridge, Massachusetts) showed how yeast can serve as "living test tubes" by supplementing them with the gene encoding the human protein alpha-synuclein—a major contributor to compromised brain function in people with Parkinson's disease. One copy of the gene didn't hurt the yeast, but two copies proved fatal. "That's when we decided to use the yeast for genetics and for drug screening," says Lindquist, who also has an appointment at the Massachusetts Institute of Technology.

In work reported in the July 21, 2006, issue of *Science*, Lindquist and her colleagues investigated whether extra amounts of any yeast gene could offset the effects of excess alpha-synuclein. They set about testing 5,000 yeast genes one by one.

The sought-after response emerged after they had tested a third of the genes in the yeast genome. Yeast bogged down by alpha-synuclein perked up when they had extra copies of genes associated with the movement of proteins from one cellular compartment to another. More specifically, these genes affect the flow of tiny fatty bubbles known as vesicles from the endoplasmic reticulum (ER), where newly made proteins are customized for special duties, to the Golgi complex, where the proteins are further modified, repackaged, and addressed for delivery. An extra copy of one particular gene rescued the yeast from alpha-synuclein overload—and, later, its counterpart did the same for roundworms, fruit flies, and rat neurons.

"It's sort of like traffic on city streets, which is normally controlled by stoplights," says Lindquist. "Here, it's like someone crashed at the intersection and nothing is getting through." The extra ER-Golgi trafficking gene acts like a police officer directing cars past the wreck. "Our idea is that [the extra alpha-synuclein] is doing something generally toxic to all cells," she says. "It's just that the dopamine-producing neurons are more sensitive and die earlier."

One hazard for these cells is the dopamine. As soon as the unstable neurotransmitter is made, vesicles must quickly package it and shuttle it out of the neuron. If dopamine accumulates inside the neuron, it can degrade into destructive by-products, such as the reactive oxygen species found in Parkinson's patients.

Collaborator (and first author of the *Science* paper) Antony Cooper at the University of Missouri–Kansas City determined that the first signs of blocked ER-Golgi traffic happen early on in yeast with an overabundance of alpha-synuclein. He also noted that the genetic boosts were rescuing yeast by, in essence, turbocharging ER-Golgi traffic to override obstruction caused by the protein.

"At that point it became really interesting," Lindquist says, "but it was just yeast."

So Lindquist called fruit fly neurogeneticist Nancy M. Bonini, an HHMI investigator at the University of Pennsylvania, to see if the findings would hold up in animals with neurons and brains. Bonini had developed a Parkinson's model by overexpressing alpha-synuclein in dopamine-producing fly neurons. She found that the gene that made the most difference in the yeast also appeared to suppress toxicity in the fly model.

"Although a yeast cell is not a neuron," Bonini says, "and nothing takes the place of [studies in] humans, this is an example of fundamental cell biology leading to a new insight that puts us in a much better position to pioneer a foundation for new therapeutic approaches."

Lindquist brought in two more collaborators late last year. Jean-Christophe Rochet at Purdue University tested the gene in midbrain neurons cultured from rat embryos, with the same results. University of Alabama researchers tried identical experiments in a roundworm model of Parkinson's disease that had been developed in the lab of Guy A. Caldwell, coordinator of an HHMI undergraduate science program.

"Lo and behold, it worked like a charm," says Caldwell, whose work is also funded by The Michael J. Fox Foundation for Parkinson's Research. "It's a beautiful continuum going from a single cell to a mammalian system. It tells us this pathway is evolutionarily conserved."

"Now we're off to the races," says Lindquist. Participating researchers are following up on promising results in their respective animal models, exploring additional features of the biology in the more complex organisms and testing small molecules from the yeast drug screen as potential new drugs. ■

– CAROL CRUZAN MORTON

FOR MORE INFORMATION: For more about the screening method developed by Lindquist and colleagues, visit the *Online Bulletin*.

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> SUSAN LINDQUIST