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Fly Studies Raise Possibility of New Treatments for Neurodegenerative Brain Disorders

Researchers have found that an enzyme that helps cells dispose of unwanted proteins may actually protect against a class of inherited brain disorders that includes Huntington's disease.

The researchers said their findings suggest that drugs or compounds that activate the protective protein, called ataxin-3, might be a possible therapy for neurodegenerative diseases that are caused by proteins whose sequences are abnormally long due to excessive repetition of the amino acid glutamine.

"This finding raises the possibility that if we can learn more about what regulates this activity of ataxin-3, such that we could use drugs to activate it, this might hold some promise for a therapeutic to slow the disease course."

— Nancy M. Bonini

The research team, led by Nancy M. Bonini, a Howard Hughes Medical Institute investigator at the University of Pennsylvania, published its findings in the April 1, 2005, issue of the journal *Molecular Cell*. Bonini's co-authors are from the University of Richmond and the University of Iowa Carver College of Medicine.

In their experiments, Bonini and her colleagues explored the role of an abnormal ataxin-3 protein in the rare inherited disorder, spinocerebellar ataxia type 3 (SCA3), which is also called Machado Joseph Disease. People with the disease experience ataxia, which causes them to lose muscle coordination, and paralysis of the eye muscles. The key question, said Bonini, was whether the normal function of the ataxin-3 protein—the protein that becomes mutated in polyglutamine disease—was central to the disorder.

"It was known that these classes of ataxias are due to an expanded polyglutamine domain in the protein, so they have a common molecular mechanism," said Bonini. "However, the expansion is in different gene

products for each disease. So one of the big questions in these diseases is how does the normal function of the protein influence the disease, if at all?"

Ataxin-3 plays an unknown role in cellular pathways that collect and destroy unwanted proteins. In these biochemical pathways, enzymes tag doomed proteins with a chainlike molecule called ubiquitin, marking them for transport to the protein-shredding proteasome. It was known only that the ataxin-3 protein has domains that bind to ubiquitin chains, that it may associate with the proteasome, and that it has ubiquitin-snipping, or "protease," activity.

Bonini and her colleagues were in a prime position to explore ataxin-3's role in SCA3, because they had developed gene-altered versions of the fruit fly *Drosophila* that carry normal and various abnormal versions of the human protein. In their studies, the researchers first found that flies with the normal version of human ataxin-3 showed no evidence of SCA3. However, the form of ataxin-3 with the polyglutamine expanded—known to be involved in human SCA3—produced a full-blown version of SCA3 neurodegeneration in the flies.

"For many human neurodegenerative diseases, one finds that the normal protein is actually also involved in the disease process," said Bonini. "But in this case, we thought, it's unusual that the normal ataxin-3 doesn't look like it's toxic at all; we couldn't see any hint that it was causing degeneration or any phenotype like the pathogenic protein.

"Then, we thought that maybe we could reveal a disease phenotype if we expressed normal ataxin-3 together with the pathogenic protein. Maybe we would see an enhancement or synergy of the pathology. But what happened, quite surprisingly, is that the normal ataxin-3 dramatically suppressed the disease. That says that the normal function of the pathogenic protein can help mitigate its own toxicity."

In further studies, the researchers tested various versions of truncated ataxin-3 for clues to its disease-suppressing role. They found that the ataxin-3 needed both its protease activity and its ability to bind to ubiquitin to protect against the pathology. Also, they found, the protein-shredding proteasome had to be functional for ataxin-3 to be protective.

Importantly, when the researchers introduced ataxin-3 into fly models of other polyglutamine diseases, including Huntington's disease, they found a similar protective effect.

"This finding raises the possibility that if we can learn more about what regulates this activity of ataxin-3, such that we could use drugs to activate it, this might hold some promise for a therapeutic to slow the disease course," said Bonini.

Bonini said the next step is to focus on understanding the mechanism of ataxin-3's protective effects. The fly will continue to be a useful model for the initial phases of drug testing. "The fly turns out to be a promising system to

use in screening for small compounds, because it has very limited blood-brain barrier for drugs,” she said. “So you can determine whether a drug works in principle in the fly, and then proceed to testing in mammals, where you can address the issue of getting the drug into the brain.”