

Too Much of Normal

A routine interaction between two proteins, when exaggerated, causes neurodegenerative diseases.



HUDA Y. ZOGHBI LONG WANTED TO know how one mutant protein can wreak such havoc in people who have spinocerebellar ataxia type 1 (SCA1). A chance observation by a first-year graduate student shed light on the problem—in what might be a case where too much good is actually bad.

SCA1 belongs to a group of neurodegenerative disorders called the polyglutamine diseases, each of which is characterized by a mutant protein with an abnormally long stretch of a single amino acid—glutamine.

“Most people have naturally focused on the polyglutamine tract [that stretch of glutamine repeats] when studying the pathogenesis of these polyglutamine diseases,” says Zoghbi, an HHMI investigator at Baylor College of Medicine in Houston. But she sees things differently. If each disorder causes a unique constellation of symptoms, Zoghbi reasons, then the shared polyglutamine tract cannot be the only part of the protein that is culpable. The challenge, then, is how to identify other regions of the protein—ataxin-1 in the case of SCA1—that contribute to the problem.

A lucky break came when first-year graduate student Matthew F. Rose was deciding whose lab to join for his dissertation work—Zoghbi’s or that of Hugo J. Bellen, also an HHMI investigator at Baylor, who works on development of the nervous system in the fruit fly *Drosophila melanogaster*. While trying out Bellen’s lab, Rose combed through the results of an experiment, designed by postdoctoral fellow Hamed Jafar-Nejad, to identify proteins that interact with the *Drosophila* protein Senseless. Rose noticed in particular that dAtx-1—the fly equivalent of ataxin-1—binds to Senseless.

Scientists knew that in humans the polyglutamine tract slows down ataxin-1 degra-

“We don’t think pathogenesis will be the result of a single protein-protein interaction. It may involve multiple interactions, some that are inconsequential, and some that are devastating for the cell.”

HUDA ZOGHBI

dation, leaving cells with too much of the mutant protein in the same way that overexpression does. But, unlike its human counterpart, dAtx-1, which was being studied by Hiroshi Tsuda, a postdoctoral fellow in the Zoghbi lab, has no polyglutamine tract. Nevertheless, when Tsuda engineered flies to make too much dAtx-1, sensory neurons were killed. This result implied that fly and human pathways might not be so different. Jafar-Nejad provided fly strains that allowed the group to study the effects of dAtx-1 on Senseless.

When Tsuda and the team investigated how excess dAtx-1 kills neurons, they found that the AXH domain—a portion of the protein conserved between flies and humans—binds directly to the Senseless protein. That interaction targets Senseless for degradation, and without Senseless the sensory neurons die. Moreover, when the team removed the AXH domain from dAtx-1, neuron death was no longer a problem.

The team then turned to a model system that is a bit more like humans than *Drosophila*—the mouse. They found

that mammalian ataxin-1 binds to growth factor independence-1 (Gfi-1), which is the mouse version of the Senseless protein; and, as in flies, too much ataxin-1 degrades Gfi-1 and leads to neuronal death. The researchers concluded that the AXH domain in mammalian ataxin-1, not the polyglutamine domain, is what is required for binding ataxin-1 to Senseless and Gfi-1. The research bolsters an emerging theory that neurodegenerative disorders can be caused by having extra copies of a normal protein, not just a mutated one.

Tsuda, Zoghbi, Bellen, and colleagues published the work in the August 26, 2005, issue of *Cell*. Harry T. Orr, Zoghbi’s research collaborator for 18 years, contributed to the work.

Other groups have found evidence that the polyglutamine tract alone does not kill neurons. Michael R. Hayden’s group at the University of British Columbia found that overexpression of a somewhat shortened huntingtin protein did not induce Huntington-type neurodegeneration in mice, even though it included a large polyglutamine stretch. But this is the first time that scientists have identified what region of the protein is necessary and understood the mechanics behind the cell death.

A lot of work remains to be done, says Zoghbi, but her team’s findings to date suggest that an exaggeration of a normal interaction between ataxin-1 and Gfi-1 causes the problem in polyglutamine diseases. The polyglutamine tract simply produces the accumulation—the exaggerated amount of ataxin-1 available for binding.

The research team—including Matt Rose, who ultimately joined Zoghbi’s lab—is now on the hunt for other ataxin-1 binding partners. ■

—Rabiya S. Tuma-

LEFT _ HIROSHI TSUDA (LEFT), HUDA ZOGHBI, AND COLLEAGUES DISCOVERED A NEW FACTOR IN THE DEVELOPMENT OF NEURODEGENERATIVE DISORDERS.

SCA1 AND HUNTINGTON’S DISEASE

While all the polyglutamine diseases kill neurons, the particular set of cells affected in each disease differs, leading to distinctive problems. For example, individuals with SCA1 gradually lose coordinated movement and speech, eventually losing control of breathing and swallowing. In contrast, patients with Huntington’s disease have tremors as well as emotional and intellectual disturbances.

ON THE WEB:

For more information about polyglutamine diseases, visit www.hhmi.org/biointeractive/neuroscience/polyglutamine_disease.html.