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Rare Genetic Disease Offers Clues to Neurodegeneration

Researchers studying a rare neurodegenerative disorder have uncovered a pathological mechanism that may also underlie more common neurological diseases, including Huntington's disease and Alzheimer's disease.

The researchers, led by Howard Hughes Medical Institute investigator Huda Zoghbi, found evidence for a kind of see-saw mechanism that modulates the ability of a mutant protein to work with its partners in the cells of patients with the rare genetic disorder known as spinocerebellar ataxia type 1 (SCA1). The new research shows that the disease can be driven not only by excessive functioning of a protein complex involving the mutant ataxin 1 protein, but also by the dampening of another protein complex due to decreased levels of normal ataxin 1.

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— Huda Y. Zoghbi

The finding has implications for how researchers think about other neurodegenerative diseases, said Zoghbi. We have always thought of these diseases as caused purely by a gain of function produced by the abnormal protein. But I think now we have to really revisit our analyses of these neurodegenerative diseases, with the perspective that for every gain there will be a loss of function elsewhere. Everything happens at a price, she said.

Zoghbi, who is at Baylor College of Medicine, and her colleagues published their findings in an advanced online publication of the journal *Nature* on March 12, 2008. The paper will be printed in the journal's April 10, 2008, issue. Zoghbi's co-authors on the paper are at Harvard Medical School, the University of Minnesota, and Vanderbilt University.

People with SCA1 suffer damage to Purkinje cells in the brain's cerebellum caused by a toxic buildup of the ataxin 1 protein, which impairs balance and

motor coordination. Loss of muscle control worsens steadily until patients are no longer able to eat or to breathe.

In earlier studies, Zoghbi and colleague Harry Orr, who is the other senior author of the *Nature* paper, showed that SCA1 is caused by a genetic stutter in which a mutation causes a segment of the ataxin 1 gene to repeat itself. The stuttering gene produces a protein with unusually long repetitive stretches of the amino acid glutamine. The researchers showed that this abnormal ataxin 1 accumulates in the nucleus of Purkinje cells, where it impairs function. SCA1 is one of nine related neurodegenerative diseases—the best known of which is Huntington's disease—caused by this type of stutter.

Zoghbi said researchers have not known how the glutamine causes the symptoms of SCA. For a long time the field focused on the glutamine repeats themselves as the toxic moiety—since in these diseases the proteins are unrelated, but the glutamine repeats are common to all of them. However, other studies had found that to be toxic, mutant ataxin 1 needed to undergo a chemical modification called phosphorylation. Toxicity was associated with phosphorylation at a specific site on the protein - the 776th amino acid, S776. The researchers reasoned that both the glutamine repeats and phosphorylation at S776 could influence ataxin 1's ability to link to other proteins. So they conducted a search for proteins whose attachment to ataxin 1 depended on both these properties. That search, using biochemical and molecular techniques, yielded a protein called RBM17.

Experimenting with cerebellar tissue as well as cells in culture, the researchers confirmed that ataxin 1 and RBM17 formed stable complexes. Most importantly, their studies revealed that the ataxin 1-RBM17 complex formed independent of an entirely different complex between ataxin 1 and a gene-controlling protein called capicua.

We found that these two complexes are mutually exclusive, which means when ataxin 1 is with RBM17, it is not with capicua, and vice versa, said Zoghbi. So, if the mutant protein preferentially interacts with RBM17, that happens at a cost. Enhancing one interaction reduces the other.

The researchers investigated the relationship between ataxin-1, RBM17, and capicua in a mouse model of SCA1, and observed a see-saw effect in which the increase in the ataxin 1-RBM17 complex and the reduced ataxin 1-capicua complex both contributed to disease pathology, said Zoghbi.

People with these disorders have both mutant and normal versions of ataxin 1, said Zoghbi. So, this finding is significant because it tells us that having enough of the normal protein is important because it is the only form left to interact with proteins like capicua, which the expanded form does not prefer to interact with. Thus, any therapeutic strategy aimed at lowering the level of mutant ataxin-1, or a polyglutamine protein in other such diseases, must avoid affecting the normal version. An effective therapy has to selectively lower the glutamine-expanded form, which is very tricky because if by accident you lower the normal form you are going to make the disease worse.

The finding in SCA1 is likely relevant not only to the other polyglutamine diseases such as Huntington's disease, but also to diseases such as Alzheimer's disease and Parkinson disease, said Zoghbi. Both those diseases are caused by abnormal accumulation of a toxic protein. There are already clues that some of these other proteins may lose interaction with normal protein partners when they develop abnormally preferential interactions with other partners in protein complexes, she said.

Zoghbi said researchers studying Alzheimer's disease, Huntington's disease, and related disorders should consider exploring which protein interactions are lost due to the mutant protein, as well as which interactions are abnormally enhanced.

In the case of SCA1, she said, further studies will concentrate on how the imbalance in the protein complexes compromises brain cells' biological machinery and ultimately kills them. And to aid treatment of SCA1, the researchers will explore whether inhibiting S776 phosphorylation could weaken the ataxin 1-RBM17 interaction, alleviating the disease by restoring the normal balance with the ataxin 1-capicua interaction.