

MAY 19, 2006

## Networking Provides New Clues to Diseases that Attack the Nervous System

Researchers at the Howard Hughes Medical Institute are unveiling a new resource that they say will speed scientists' understanding and treatment of a group of inherited disorders called ataxias that kill cells in the brain, causing loss of balance, coordination and often death. The scientists are making new data available on hundreds of interacting proteins that are involved in dozens of inherited forms of ataxia.

The approach to mapping the global set of interacting proteins—called an interactome—could also be applied to disorders as diverse as Parkinson's disease, diabetes, and hypertension.

---

"Very little was known about the normal functions of the proteins involved in inherited ataxias and how those functions might contribute to the disorders. And while there were bits of information on each of these proteins, since investigators were working in isolation, there was little understanding of how they might be involved in common pathways whose malfunction leads to the pathologies of these disorders."

— **Huda Y. Zoghbi**

---

Howard Hughes Medical Institute investigator Huda Y. Zoghbi and her colleagues reported on their studies in an article published in the May 18, 2006, issue of the journal *Cell*. Zoghbi and her colleagues at the Baylor College of Medicine collaborated on the studies with researchers from Harvard Medical School and the University of Notre Dame.

Since proteins are the major machines that work inside cells, understanding how they interact may give researchers an opportunity to learn how they can go awry and cause disease. Furthermore, understanding these interactions offers scientists targets for drugs that can help restore normal function to such malfunctioning machinery.

Very little was known about the normal functions of the proteins involved in inherited ataxias and how those functions might contribute to the disorders, said Zoghbi. And while there were bits of information on each of these proteins, since investigators were working in isolation, there was little understanding of how they might be involved in common pathways whose malfunction leads to the pathologies of these disorders, she said.

To map the interaction of proteins involved in the ataxias, the researchers started with 54 proteins that were either directly involved in known diseases, or that were associated with those causative proteins. The researchers then screened those proteins for interactions with proteins produced by two huge libraries of human genes, including one library of genes specifically associated with the brain.

To detect these interactions, the researchers used the yeast two-hybrid assay—a technique invented by HHMI researcher Stanley Fields at the University of Washington. The assay involves attaching proteins to either of two separated components of a protein known as a transcription factor that switches on a telltale marker gene inside yeast cells. If the two proteins interact within the yeast cells, the transcription factor components are brought together, and the marker gene is activated.

The researchers' screening revealed some 770 interactions between the ataxia proteins and those in the libraries. According to Zoghbi, the vast majority of these interactions had never been detected by researchers before. To test the validity of these findings, the researchers directly determined whether a sample of these interactions actually occurred in mammalian cells. Those experiments showed that more than 80 percent were valid interactions in cells. What's more, when they explored the scientific literature for known interactions between the proteins they had identified, they found 4,796 additional protein-protein interactions.

The protein interaction network has already given the researchers insight into the function of the disease-related proteins, said Zoghbi. She and her colleagues found that many of the proteins on their map were involved in RNA transcription and processing and protein degradation. That finding tells us these are processes that are probably very important for Purkinje cell integrity and that somehow perturbation of these processes is responsible for their degeneration, said Zoghbi.

Another key finding, said Zoghbi, was that certain proteins seemed to be hub proteins in the networks - interacting with many other proteins. Studying these hub proteins could yield insight into both the basic workings of Purkinje cells, which are important to the part of the brain that integrates sensory input with motor output, and how the many ataxia-causing proteins

cause the common pathologies that destroy them. Understanding the function of the hub proteins could yield basic insight into the machinery of Purkinje cells, she said.

Importantly, said Zoghbi, the researchers found that that many proteins that animal studies had indicated either aggravate or reduce the effects of ataxia proteins showed direct physical interactions with the disease proteins in their interaction map. Identification of these genetic modifiers is important, said Zoghbi, because they might prove effective targets for drugs to treat ataxias. Such findings can enable us to prioritize which modifiers we should be studying, she said. Perhaps if we study these direct interactors, we can identify the processes that are directly impacted by the mutation and learn to affect them with drugs.

Overall, said Zoghbi, the ataxia protein-protein interaction network will enable a far more strategic approach to studying the diseases. The technique of starting with known disease-causing proteins and developing interaction networks could yield invaluable insights into such disorders as Parkinson's disease, diabetes, and hypertension.

If you start with sets of genes known to be directly involved in such diseases and develop a network around them, you can begin to identify proteins that contribute to susceptibility to the diseases, said Zoghbi. This susceptibility might affect not just people with inherited forms, but also those in the general population. And, the proteins identified might turn out to be more amenable to manipulation by a pharmacologic agent than the causative protein itself.

Zoghbi plans to apply the insights from the protein interaction network to study those that interact with Ataxin-1. Mutations in Ataxin-1 are known to cause the rare neurodegenerative disorder spinocerebellar ataxia type 1. She will also concentrate on deciphering the functions of the hub proteins. We would hope that the investigators studying other ataxias will find this network similarly useful in their research efforts, she added.