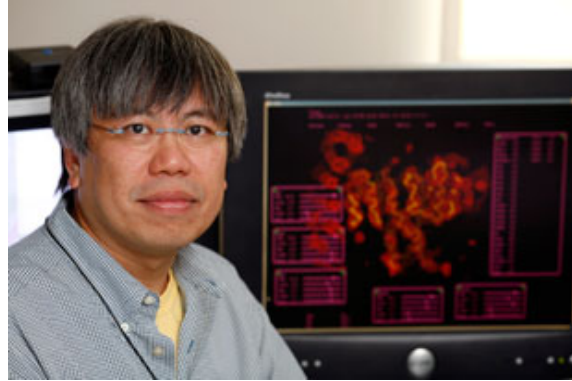


Indiana University Researchers Get NIH funding For HD research

The National Institute of Health has awarded a \$1.2 million four year research grant to Dr. Joel Ybe of the Indiana University to study how aberrant protein interactions lead to cell death in Huntington's Disease. Dr. Ybe, a structural biologist will work with IU Bloomington chemist David Giedroc to learn more about these proteins through nuclear magnetic resonance technology.

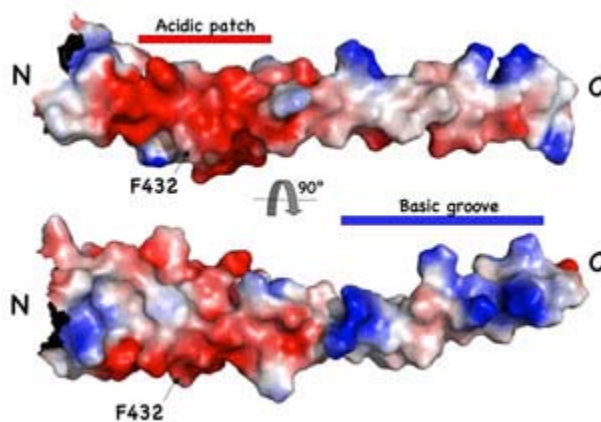


Dr. Ybe, Photo by Chris Meyer

The huntingtin's protein interacts with at least 234 other proteins. Abnormal protein interactions have long been thought to contribute to the disease. Dr. Ybe's research will investigate the interactions among the Huntingtin Interaction Protein, the Huntingtin Interaction Protein 1 interactor, and clathrin.

The Huntingtin Interacting Protein (HIP1) was discovered in 1997 in Michael Hayden's lab at the Department of Medical Genetics, University of British Columbia, Vancouver, Canada, and simultaneously in the Max Planck Institute for Molecular Genetics in Berlin, Germany.

The research grant will allow Dr. Ybe to continue the work that he began with colleague Quin Niu and published in 2008. The highly technical article presented new information about the structure of HIP1. The huntingtin's protein is supposed to bind with HIP1 on a particular site on HIP1. The HD mutation, however, does not. Instead another protein, called Huntingtin's Interaction Protein 1 interactor (HIPPI) comes in and binds to that particular site and the interaction of HIP1 and HIPPI appear to lead to cell death.



This image shows the critical, negatively charged HIPPI binding region in red next to a positively charged region in blue. The nitrogen and carbon termini of the protein segment are shown as "N" and "C," respectively.

The way that this might work is through the disruption of the process of cell nutrition. Right next to the site where HIPPI is binding is the site where a protein called clathrin binds. Clathrin surrounds needed nutrients and brings them into the cell. HIP1 then distributes them where they are needed. If HIPPI disrupts this process, it could be an important source of HD pathology.

Dr Ybe explained that the goal of the new research is "to define the molecular basis for how the interaction between clathrin-coated vesicles and HIP1 is regulated in healthy cells," Ybe said. "The successful completion of our upcoming studies will give us an unprecedented atomic-level understanding of HIP1 function in cellular trafficking and my hope is that they will inform and stimulate many areas of Huntington's disease research."

Knowing the structure of proteins is important in drug design - so this research could lead to treatments if the theory is correct.

By understanding the three-dimensional pocket of HIP1 that HIPPI binds to, Ybe says scientists could devise a way to disrupt the binding event in the first place, which could in turn prevent Huntington's disease from progressing. That disruptor could be a small protein drug that is engineered to fit into the HIPPI binding pocket but does not interfere with the cell's other natural processes. But such a treatment could only come about by gaining an intimate understanding of the shape and chemical properties of the HIP1 binding pocket.

Referemces

Qian Niu and Joel A. Ybe. "**Crystal structure at 2.8 Å of Huntingtin-interacting protein 1 (HIP1) coiled-coil domain reveals a charged surface suitable for HIP1 protein interactor (HIPPI).**" *Journal of Molecular Biology* 2008 Feb 1, 375(5):1197-205.

- *Marsha L. Miller, Ph.D., April 30.2009*

Photo and illustration are courtesy of the University of Indiana.