

Metalloproteinases are new targets

Dr. Lisa Ellerby, Dr. Robert Hughes, and colleagues at the Buck Institute for Age Research have identified a group of proteinases as promising new targets for treatment. Proteinases are enzymes which cleave proteins.

The approach was based on the toxic fragment hypothesis that has received much support in previous research studies. The idea is that a key event in the development of Huntington's Disease is the cleavage of the HD protein into fragments which then enter the nucleus of the cell and cause damage.

Since the huntingtin's protein is a caspase substrate, research into protein cleavage has focused on the cysteine protease family of caspases and calpains. Research by Dr. Michael Hayden and colleagues showed that when HD mice are crossed with mice genetically engineered to lack caspase six, they do not develop Huntington's Disease. Researchers have been working on developing a safe and effective caspase six inhibitor but do not have one so far.

The researchers decided to use an unbiased approach to identifying proteinases whose inhibition could be neuroprotective. Using high throughput screening technology, they knocked down each of the 514 known or suspected proteinase genes in HD cell cultures with siRNA and identified eleven whose suppression limited the accumulation of HD protein fragments. Nine of these are expressed in striatum cells and their suppression reduced cellular toxicity in a secondary screen.

Of the nine remaining, three of these were matrix metalloproteinases (MMPs), zinc-containing enzymes whose function is to degrade extracellular matrix proteins. These were of particular interest because inhibitors of metalloproteinases are already in drug development for treating a variety of diseases. An imbalance between MMPs and tissue inhibitor metalloproteinases (TIMPs) has been implicated in cancer, kidney disease, rheumatoid arthritis, and heart disease. Inhibiting MMPs has also been shown to limit neuronal damage after stroke.

The researchers found that MMP enzymatic activity is elevated both in the R6/2 mice and the YAC128 mouse models of HD. One of these, MMP10, was found to directly cleave the HD protein. They found that the cleavage occurred at amino acid 402. Knocking down MMP10 prevented cell death in striatal cells with the HD protein.

The researchers also tested their approach in a drosophila model of HD. Drosophila has only two MMP genes and only the second (Dm2-MMP) is expressed in the brain. Knocking this gene down improved motor impaired. In addition, the HD protein also causes neurodegeneration of photoreceptors in the eye. Knocking down the Dm2-MMP gene partially ameliorated the problem.

Further research is likely to proceed quickly. "We've found a target that has known drugs for cancer treatment that could possibly have significance for HD," said Dr. Ellerby. "MMPs are also involved in stroke, inflammation and many neurological processes; we expect a lot of scientific attention to now be focused on this important class of proteases," she said.

"The next step in this research will be to test some of the MMP inhibitor drugs as a potential treatment in HD mouse models," said Dr. Ellerby. "We'll also be crossing mice that no longer have particular MMPs with those who have HD to see what effect that has on offspring," she said.



Reference:

John P. Miller, Jennifer Holcomb, Ismael Al-Ramahi, Maria de Haro, Juliette Gafni, Ningzhe Zhang, Eugene Kim, Mario Sanhueza, Cameron Torcassi, Seung Kwak, Juan Botas, Robert E. Hughes, and Lisa M. Ellerby. **“Matrix Metalloproteinases Are Modifiers of Huntingtin Proteolysis and Toxicity in Huntington’s Disease/”** Neuron Volume 67, Issue 2, 199-212, 29 July 2010

- *Marsha L. Miller, July 30, 2010*