Toxic HD protein fragments

The toxic fragment hypothesis continues to be supported by the results of research by Coalition for the Cure researchers and their colleagues. 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.

The HD community was electrified in 2006 when Dr. Michael R. Hayden and colleagues reported that HD mice also engineered to be resistant to caspase-6 did not develop Huntington’s Disease.

The word caspase comes from cysteine-aspartic-acid-proteases. Caspases are enzymes which are used in apoptosis, programmed cell death. There are various caspases that initiate the process, that cleave proteins and that actually ‘execute’ the cell. Apoptosis is a necessary process in development and also in destroying tumors. Unfortunately apoptosis is also implicated in neurodegenerative disorders. Apoptosis is also triggered by cellular stress, especially mitochondrial stress, and this is known to occur with Huntington's and the various other neurodegenerative disorders.

Caspase 3 and caspase 6 both cleave the HD protein, but Dr. Hayden’s work showed that caspase 3 resistant HD mice did develop the disease while caspase 6 resistant mice did not.

Not all fragments are toxic. The strongest evidence for this comes from the development of the shortstop mouse in work by Hayden and colleagues published in 2005. (Slow et al 2005). This mouse expresses an N-terminal HD protein fragment which differs from the one generated by caspase six cleavage. Fragments did enter the nucleus of the cell in this mouse model and did form aggregates and yet there was no evidence of disease in the mouse's development or behavior and no neurodegeneration occurred. Therefore, the problem could not be fragmentation itself but would have to be the generation of specific toxic fragments.

Researchers are working on developing a caspase six inhibitor as a potential treatment. At the same time, basic research is also continuing into fragmentation since it is not clear why some fragments are so toxic and others not.

Coalition researchers Dr. Christopher Ross and Dr. Hayden are also looking at fragments from other cleavage sites and assessing their toxicity. The HD protein is subject to cleavage in two areas. One is between sites 460 and 600. Caspase 6 cleaves the HD protein at site 586. The other area is near the N-terminus of the protein.
Working with a PC12 cell model, Drs. Ross and Hayden have discovered two new N-terminus fragments, cp-1 and cp-2 (cp stands for cleavage product). Cp-1 and cp-2 fragments are produced and accumulate within nuclear and cytoplasmic inclusions prior to huntingtin-induced cell toxicity, and these fragments can be formed by caspase independent proteolytic cleavage.

They have narrowed cp-1’s cleavage site to somewhere between sites 81 and 129. They were able to determine that the cleavage site for cp-2 is at position 167. Altering that site reduced toxicity but increased aggregation.

The researchers suggest that once more is learned about fragmentation pathways, more therapeutic targets may emerge.

References:


- Marsha L. Miller, Ph.D., March 16, 2009