Protease associated with damage after stroke implicated in Huntington's toxicity

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A new study reveals that an enzyme linked with multiple disorders is also involved in the generation of toxic, neuron-killing protein fragments in Huntington's disease (HD). The research, published by Cell Press in the July 29 issue of *Neuron*, provides insight into Huntington's pathology and proposes new therapeutic strategies for this devastating incurable disease.

HD is an inherited disease that is characterized by degeneration of brain cells in the striatum and cortex. Symptoms of HD include uncontrolled movements, emotional disturbances, and mental deterioration. HD is caused by abnormal huntingtin protein (Htt), and previous research has shown that it is small fragments of mutant Htt that are the most toxic for cells.

"A number of proteases, enzymes that cleave proteins, have been shown to work on mutant Htt," explains senior study author, Dr. Lisa M. Ellerby from the Buck Institute for Age Research. "While it has been suggested that cathepsins and/or calpains are the proteases responsible for producing the smallest and most harmful fragments, the exact cleavage sites and identity of the proteases involved have not been unequivocally identified."

Dr. Ellerby, along with coauthor Dr. Robert E. Hughes and colleagues, designed a sophisticated screen to examine the generation of the smallest Htt fragments. "Our screen identified 11 proteases that, when inhibited, reduced Htt fragment accumulation," explains Dr. Hughes. "Three of

these belonged to the matrix metalloproteinase (MMP) family." MMPs have been implicated in a diverse collection of pathological processes, including rheumatoid arthritis, cardiovascular disease, cancer, and neuronal cell death after a stroke.

The researchers went on to show that one specific family member, MMP-10, directly cleaved Htt and that reduction of MMP prevented cell death in cultured striatal cells. Further, MMP activity was significantly elevated in mouse models of HD and reduced MMP activity reduced Htt-induced neuronal dysfunction in fruit flies.

Based on their findings, the researchers suggest that MMP family members should be considered as rational targets for developing novel HD therapeutics. "Our results suggest that general inhibition of MMPs may be of therapeutic benefit in Huntington's disease and that specific inhibitors of MMP-10 may be particularly relevant to disease treatment," concludes Dr. Ellerby.

More information: Miller et al.: “Matrix Metalloproteinases Are Modifiers of Huntingtin Proteolysis and Toxicity in Huntington’s Disease.” Publishing in Neuron 67, 199-212, July 29, 2010. DOI 10.1016/j.neuron.2010.06.021

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