

Modification of mutant huntingtin protein increases its clearance from brain cells

April 2 2009

A new study has identified a potential strategy for removing the abnormal protein that causes Huntington's disease (HD) from brain cells, which could slow the progression of the devastating neurological disorder. In the April 3 issue of *Cell*, a team of researchers from the MassGeneral Institute for Neurodegenerative Disease (MGH-MIND) describes how an alteration to the mutated form of the huntingtin protein appears to accelerate its breakdown and removal through normal cellular processes.

"Using Huntington's disease as a model, we identified a mechanism whereby modification of the disease-causing protein itself facilitates the cell's own method of digesting and recycling the mutant protein," says Dimitri Krainc, MD, PhD, of MGH-MIND and the Massachusetts General Hospital (MGH) Department of Neurology. "This enhanced clearance improved neuronal functioning and prevented neurodegeneration in cellular and animal models."

HD is an inherited disorder caused by a mutation in the gene for a protein called huntingtin. Deposits of the <u>abnormal protein</u> accumulate within the brain, leading to the degeneration and death of <u>brain cells</u>. Symptoms of HD, which usually begin to appear in the middle years, include uncontrolled movements, erratic emotions and problems with thinking and memory. Symptoms worsen over the 10- to 30-year course of the disorder, until patients die from a variety of complications.

Studies of mutant huntingtin by MGH-MIND researchers and their



collaborators suggested a possible connection with a process of protein modification called acetylation, in which enzymes add a molecule called an acetyl group to the amino acid lysine. While the acetylation of histones, proteins involved in <u>gene regulation</u>, has been known for 40 years, it only recently has been discovered that other proteins are also acetylated, suggesting that the process has a broader array of functions. After discovering that mutant huntingtin interacts with known acetylation-inducing enzymes, the MGH-MIND team set out to investigate whether acetylation has a role in the disease.

After first confirming that mutant huntingtin is acetylated by a specific group of enzymes, the researchers showed that mutant protein made resistant to acetylation formed significantly larger deposits in mouse brains and was more toxic than acetylation-sensitive huntingtin. In a C. elegans roundworm model of HD, acetylation of mutant huntingtin significantly reduced neurodegeneration. Other experiments indicated that acetylation accelerates clearance of the mutant protein from cells by means of autophagy - a natural cellular process for digesting and removing unnecessary or abnormal proteins and other components.

A key observation was that acetylation, while increasing the removal of mutant huntingtin, had little effect on the normal version of the protein. "One of the major challenges of research into neurodegenerative disorders like Huntington's, Alzheimer's and Parkinson's diseases - all of which involve accumulation of proteins within the brain - has been how to activate degradation machinery that only removes the disease-causing proteins and leaves normal proteins untouched," Krainc explains.

"Among several candidate HD drugs currently in development are some that increase acetylation, but we need to identify more specific versions of these drugs that target only the mutant protein and don't affect other cellular pathways. In addition to huntingtin, we are examining whether acetylation of other disease-associated proteins affects their degradation



and are interested in the detailed molecular mechanisms responsible for the recognition of acetylated proteins by the autophagic degradation machinery," he adds. Krainc is an associate professor of Neurology at Harvard Medical School.

Source: Massachusetts General Hospital (<u>news</u> : <u>web</u>)

Citation: Modification of mutant huntingtin protein increases its clearance from brain cells (2009, April 2) retrieved 5 May 2024 from https://medicalxpress.com/news/2009-04-modification-mutant-huntingtin-protein-clearance.html

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