'Intrabody' can mop up mutant protein in Huntington's disease model

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Scientists have created a tool for mopping up the clumps of mutant protein that drive neurodegeneration in Huntington's disease. Emory University researchers engineered a virus to make an intracellular antibody or "intrabody" against huntingtin, the protein whose mutant forms poison the brain cells of people with Huntington's.

Injecting the virus into the brains of mice that make mutant huntingtin improves their ability to move their limbs, although it does not prolong their lives.

The results will be published online and are scheduled for publication in the May/June issue of the *Journal of Cell Biology*.

Although other researchers have shown that various intrabodies can protect cells from mutant huntingtin, the Emory team was the first to examine the effects of an intrabody in living mice, says senior author Xiao-Jiang Li, PhD, professor of human genetics at Emory University School of Medicine.

Delivering the intrabody to brain tissues in people would be a formidable challenge, because it would require some form of gene therapy. However, it may be possible to use information about the intrabody's structure to find drugs that mimic its effects, Li says.

Huntington's affects about 30,000 people in the United States and usually begins in young- to mid-adulthood with the slow destruction of

brain cells, leading to involuntary movements, cognitive impairment and sometimes depression or paranoia. Another 150,000 people are believed to have mutations that cause the disease, but have not begun to show clinical symptoms. The disease is fatal and currently there is no way to slow its development, although some medications can alleviate symptoms.

Disease-causing mutations involve a lengthening of part of the gene for huntingtin, so that it repeats three letters (CAG) of the genetic code dozens of times. Mutant proteins have a region consisting of the same amino acid (glutamine) many times, called poly-glutamine, which makes the proteins clump together inside brain cells.

Li says scientists who work on Huntington's have been studying where inside the cell the clumps have their toxic effect: brain cells' nuclei or in their axons and dendrites.

"Our goal here was to create a tool that could distinguish between the accumulation of mutant proteins in the nucleus and the cytoplasm," he says. "The intrabody binds huntingtin proteins with expanded poly-glutamine regions and it only works in the cytoplasm, not the nucleus."

Li and his colleagues showed that cultured cells that make both the intrabody and mutant huntingtin are able to get rid of the mutant protein faster and have fewer clumps of huntingtin.

Even though the intrabody only travels within the cytoplasm, it still alleviated the motor problems of mice that make mutant huntingtin when injected into the striatum, the scientists found. The striatum is the part of the brain most affected by Huntington's disease.

Li says finding an antibody that prefers to bind mutant, aggregated protein could also prove useful in the study of other neurodegenerative

disorders, such as Alzheimer's disease or Creutzfeldt-Jakob disease.

"Several neurodegenerative diseases appear to involve defects in protein folding and metabolism, leading to the accumulation of protein aggregates inside cells," he says. "Our study suggests a strategy for dissecting the harmful effects of these protein aggregates in other diseases."

The clumps of mutant huntingtin are also seen in the neuronal nucleus and cytoplasm in a recently established transgenic monkey model of Huntington's, which was reported by Emory University researchers: www.physorg.com/news130337949.html .

Source: Emory University