Subtle change dramatically reduces pathogenic potential of Huntington's protein

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Scientists have identified a key molecular switch that may drive the onset of Huntington's disease (HD), an incurable neurodegenerative disorder that leads to severe disruptions in muscle coordination and cognitive function. The research, published by Cell Press in the December 24 issue of the journal Neuron, enhances the understanding of HD pathogenesis and may direct new strategies for treating this devastating brain disease.

HD is caused by an abnormally lengthy repeating stretch of the amino acid glutamine within a large protein called huntingtin (htt). Huntingtin is thought to function as a kind of molecular scaffold that mediates many intricate cellular processes. "It's unclear how the mutant protein causes age-related and progressive loss of brain cells in patients with Huntington's disease," explains senior study author X. William Yang, M.D., Ph.D., of the Jane and Terry Semel Institute of Neuroscience and Human Behavior at David Geffen School of Medicine at UCLA. "Our study explored whether regions of the protein besides the polyglutamine mutation play a role in the development of the disorder."

Recent work has revealed that two specific amino acids in htt, serine 13 (S13) and serine 16 (S16), can be phosphorylated. Phosphorylation is a relatively common signaling mechanism that enables proteins to be regulated via attachment of phosphate groups to specific amino acids. To investigate the importance of phosphorylation to disease pathogenesis in a mouse model of HD, Dr. Yang and colleagues introduced mutations that elicited or prevented phosphorylation of full-length mutant htt

(mhtt). Specifically, they replaced the S13 and S16 with phosphomimetic aspartate (SD) or phosphoresistant alanine (SA).

The researchers found that full-length mhtt induced motor and psychiatric-like behavioral deficits, mhtt aggregation, and selective neurodegeneration in the SA mice but that these pathological changes were absent in the SD mice. In addition, SD mutations had a dramatic impact on the process of mhtt protein aggregation while SA mutations did not. Taken together, the findings demonstrate that subtle molecular changes of only two amino acids in full-length mhtt dramatically reduced the pathogenic potential of the mutant protein.

"It is now crucial to understand how subtle modifications in this critical molecular switch can have such a profound impact on disease pathogenesis," said Yang. "It is also important to screen for drugs that can enhance or mimic the effects of phosphorylation which may help to detoxify the mutant huntingtin protein and prevent the onset of HD."

More information: Gu et al.: “Serines 13 and 16 Are Critical Determinants of Full-Length Human Mutant Huntingtin Induced Disease Pathogenesis in HD Mice.” Publishing in Neuron 64, 828-840, December 24, 2009. DOI 10.1016/j.neuron.2009.11.020

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