# IKK may act as both inhibitor and promoter of Huntington's disease

December 21 2009

The kinase IKK phosphorylates the protein mutated in Huntington's disease to promote its removal and neuron survival, but IKK may be a double-edged sword that increases neurotoxicity in later stages of the disease. The study, led by researchers from the University of California, Irvine, will be published online December 21 in the Journal of Cell Biology.

Huntington's disease is caused by an expanded polyglutamine repeat in the protein Huntingtin (Htt), which causes the protein to aggregate and damage neurons. Ubiquitination and SUMOylation of Htt's N-terminal domain affect the protein's stability and toxicity, but other post-translational modifications in this region of the protein might be important as well.

Thompson et al. discovered that the inflammatory kinase IKK phosphorylates Htt, altering the complex pattern of SUMOylation, ubiquitination, and acetylation on neighboring lysine residues. The net result was to promote Htt's degradation by both the proteasome and lysosomes. Lysosome-mediated degradation of Htt was blocked by knocking down the autophagy proteins LAMP-2A and Atg7. Compared to wild type, mutant Htt with an expanded polyglutamine stretch was degraded inefficiently, but a version that mimicked IKK phosphorylation with negatively charged aspartate residues was still less toxic to neuronal slice cultures.

But there may be a darker side to IKK phosphorylation—it also targets

Htt to the nucleus where, says senior author Joan Steffan, a particularly toxic fragment that enhances neurodegeneration may accumulate. IKK may thus be involved in both clearing Htt and in generating a more dangerous version of the protein. The latter pathway would predominate in older patients because proteasome and lysosome function declines with age. Therapies aimed at IKK might need to either enhance or block the kinase's function, depending on the patient's age and stage of disease.

**More information:** Thompson, L.M., et al. 2009. J. Cell Biol. doi:10.1083/jcb.200909067

Provided by Rockefeller University