

Acetylation of the HD protein enhances clearance

Researchers from Massachusetts General Hospital's Institute for Neurodegenerative Disease have developed a new strategy for treating Huntington's Disease by showing that enhancing the acetylation of the HD protein will tag it for clearance through autophagy. Acetylation involves the attachment of an acetyl group to a protein to modify its activities.

The huntingtin's protein is normally found in the cytosome of the neuron. The HD version of the protein enters the nucleus and accumulates there causing problems such as the alteration of the transcription of other genes. If a safe and effective drug could be developed to enhance the clearance of the HD protein out of the nucleus, it would likely be a major treatment for the disease.

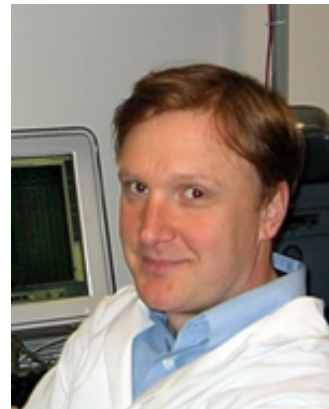
The normal huntingtin's protein is cleared away through the Ubiquitin Proteasome System (UPS) in which proteins which are not needed or which have misfolded are tagged for degradation by a small protein called ubiquitin. The unwanted protein is then moved into the proteasome, a barrel like protein complex, which breaks it down into amino acids that can then be recycled.

In Huntington's Disease, the UPS is impaired and is unable to handle the HD protein. There's an alternate system of protein degradation called autophagy which literally translates as 'self eating.' In this very old cellular house cleaning process (it's found in organisms from yeast to mammals), damaged parts of the cell, pathogens, and large proteins are surrounded and consumed.

However, autophagy is available only in the cytosome. Enhancing it might be a partial treatment because it could at least clear away the HD protein in the cytosome where it causes some toxicity but it would not take care of the accumulating protein in the nucleus which is a much larger problem. An additional difficulty is that enhancing autophagy generally would very likely have some negative effects through its actions on other proteins that are needed to do the work of the cell.

Working with both a cell model and a *c. elegans* (worm) model of HD, Dr. Dimitri Krainc and colleagues found that the HD protein is acetylated at lysine 444 while the normal huntingtin's protein is not. Interestingly, this area of the protein is found on the toxic fragments generated by caspase six. Inhibiting acetylation led to even more nuclear accumulation and made the disease process worse in HD mice suggesting that this is a cellular defense mechanism.

They then investigated whether enhancing acetylation would improve protein clearance. They found that upregulating the CREB binding protein (CBP) enhanced acetylation and reversed the toxic effects of the HD protein in a cell model and the *c. elegans* model of the disease.



They also found that the acetylated HD protein left the nucleus of the cell, returned to the cytosome and was degraded through autophagy. They also identified the protein P62 (which is known to co-localize with the HD protein aggregates) as having a role in the process. Knocking down its expression by 40 percent significantly reduced the protein clearance.

"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.

Drug discovery or development will be necessary for this new strategy to come to fruition. A Novartis scientist participated in the research suggesting that the company may be interested in working with MGH-MIND on this project. At a 2008 Hereditary Disease Foundation, Novartis discussed its efforts to find treatments for Huntington's Disease.

Reference

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- *Marsha L. Miller, Ph.D., April 20, 2009*