

Cargo Recognition is Impaired in Autophagy in Huntington's Disease.

One of the major pathologies in Huntington's Disease is the accumulation of the toxic huntingtin protein in both the cytosol and the nucleus of the affected neurons where it causes damage leading to cellular dysfunction and cell death.

There are two methods by which cells degrade and recycle proteins. One is through the Ubiquitin Proteasome System (UPS) in which proteins that are not needed or that 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. The normal huntingtin protein is degraded in the cytosol through the UPS.

However, in Huntington's Disease, the UPS is unable to handle the HD protein properly. 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 by autophagosomes. The autophagosomes deliver their cargo to the lysosomes by fusing with them. The lysosomes then consume the material.

The mutant huntingtin protein is removed from the cytosol through autophagy. This process is unavailable in the nucleus of the cell which depends on the UPS. One suggested strategy for treatment is to enhance autophagy to at least deal with the problems caused in the cytosol. And indeed, studies have shown an increase in autophagy occurs in response to the mutant protein.

So why is the HD protein accumulating in the cytosol?

Researchers at Albert Einstein Medical College in New York City have carefully examined the autophagy process in various cell models derived from two HD mouse models and HD patients. As did other researchers, they found an increase in autophagosomes in tissue from HD patients. They also found that the autophagosomes form normally and fuse normally with the lysosomes. In a seeming paradox, however, they found a reduction in proteolysis (the breakdown of proteins) in both the striatal and non-neuronal HD cells that they examined.

“Studies have shown that Huntington's disease occurs in part because the mutated huntingtin protein accumulates within cells and is toxic to them,” said Ana Maria Cuervo, M.D., Ph.D., professor of developmental and molecular biology, of anatomy and structural biology, and of medicine at Einstein and senior author of the *Nature Neuroscience* study. “In our investigation of how the accumulating huntingtin protein affects the functioning of cells, we found that it interferes with the cells' ability to digest and recycle their contents.”

Dr. Cuervo and her team discovered that the defective huntingtin proteins stick to the inner layer of autophagosomes, preventing them from gathering garbage. As a result, the

autophagosomes arrive empty at the lysosomes. They found an enhanced binding of the HD protein with P62 at the autophagic membranes. Since P62 appears to be necessary for the autophagosomes to recognize cellular garbage, this could explain the problem.

The researchers also found an increase in abnormal lipids and depolarized mitochondria which may be caused, in part at least, by the autophagosomes failure to recognize them as material (or cargo) for degradation and recycling. Their ongoing presence could contribute to the damage that leads to cell death.

This research shows that enhancing autophagy will not work as a treatment. “It doesn’t matter how active your lysosomes are if they’re not going to receive any cellular components to digest,” she said. “Instead, we should focus on treatments to help autophagosomes recognize intracellular garbage, perhaps by minimizing their contact with the defective huntingtin protein. By enhancing the clearance of cellular debris, we may be able to keep Huntington’s patients free of symptoms for a longer time.”

Reference:

Marta Martinez-Vicente, Zsolt Talloczy, Esther Wong, Guomei Tang, Hiroshi Koga, Susmita Kaushik, Rosa de Vries, Esperanza Arias, Spike Harris, David Sulzer & Ana Maria Cuervo. “ **Cargo recognition failure is responsible for inefficient autophagy in Huntington’s disease.**” Nature Neuroscience 2010 Apr 11. [Epub ahead of print]

- *Marsha L. Miller, April 14, 2010*