NEURODEGENERATIVE DISEASE

‘Empty’ autophagosomes fail to carry their cargo in Huntington disease

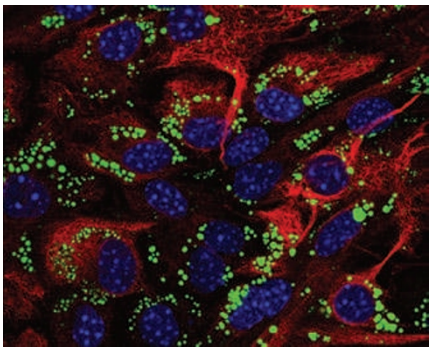
An autophagy defect in which autophagosomes fail to recognise their correct cargo could underlie the pathogenesis of Huntington disease (HD), according to new research led by Ana Maria Cuervo from the Albert Einstein College of Medicine, Bronx, NY, USA. “The autophagosomes form properly and fuse with lysosomes, [but] they are not efficiently sequestering the cargo that needs to be recognized,” says Cuervo.

> “...interaction of the mutant protein with autophagy components seems aberrant”

Autophagy maintains cellular homeostasis, and when this quality control system malfunctions homeostasis is altered and cells can ultimately lose their function and viability. Defects in macroautophagy—a process in which cellular components become engulfed in double membrane vesicles called autophagosomes—are thought to be involved in the development of HD, although the exact mechanism is poorly understood. A relationship is proposed to exist between huntingtin, the mutant form of which is toxic to brain tissue and causes HD, and autophagy. In addition, increased numbers of autophagosomes have been observed in the affected neurons in several neurodegenerative disorders, including Alzheimer disease, Parkinson disease and prion disorders.

To investigate the role of autophagy in HD, Cuervo and her colleagues used a number of mouse models of the disease, as well as cellular models (including striatal cell lines and primary neuronal cells), and lymphoblasts and brain biopsy samples (from striatal tissue) from patients with HD. In the many cell types and HD models tested, the scientists showed that the mutant form of huntingtin impaired macroautophagy and decreased the rate of intracellular protein degradation.

The formation of autophagosomes was unaffected by mutant huntingtin: autophagosomes formed at normal or even increased rates, and could be degraded by lysosomes as usual. Using both morphological and biochemical analysis, however, the investigators found that autophagosomes in HD cells were ‘empty’, and that these empty vesicles accumulated in the cytosol and failed to correctly recognize and trap cytosolic cargo. This impaired cargo recognition led to increased numbers of lipid droplets and altered mitochondrial turnover in the cytosol of HD cells compared with controls, all of which could contribute to cellular toxicity and damage.



Accumulation of lipid droplets (green) in cultured cells from Huntington disease models (cytoskeleton, red; nucleus, blue). Image provided by Prof. Ana Maria Cuervo.

“The reason for the failure in cargo recognition seems to be the abnormal association of mutant huntingtin with autophagosomes,” concludes Cuervo. “The wild-type protein also localizes normally in this compartment but the interaction of the mutant protein with autophagy components seems aberrant.” The researchers will now investigate the role of wild-type huntingtin in autophagy and hope that this research will lead to new therapeutic approaches for HD.

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