

UPS impairment and HD

The initials UPS usually stand for United Parcel Service, but in HD research UPS means the Ubiquitin Proteasome System. In this system, 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.

The UPS appears to be impaired in HD and it doesn't appear to be able to handle the HD version of the protein very well. More needs to be learned about the role of the UPS in Huntington's Disease such as the association between the UPS and inclusion bodies (the protein aggregates), and whether it is possible to ameliorate its impairment. Two new studies have addressed some of the questions.

Dr. Steven Finkbeiner and colleagues have added to our knowledge about the Huntington's Disease through the use of a robotic microscope he developed that allows researchers to track events in living cells over time. As is already known, some cells form inclusion bodies (IBs) in the nucleus and some do not. They discovered that IBs form in the nucleus of those cells where the UPS is more impaired. Once the IBs form, the UPS then becomes less impaired. This supports the idea that the inclusion bodies are neuroprotective rather than a major cause of pathology.



Dr. Atsushi Iwata and colleagues at the University of Tokyo have also been researching the UPS. They refer to the UPS as "the front line of protein quality control." There is an alternate system of protein degradation called autophagy which can degrade the HD protein in the cytoplasm, but their work has shown that this system is unavailable in the nucleus where the mutated protein accumulates and causes a cascade of problems.

Dr. Iwata and colleagues have identified the ubiquitin ligase UHRF-2 as capable of enhancing the degradation of the HD protein in the aggregate form in cell nucleus. An ubiquitin ligase is a protein that attaches the ubiquitin to a target protein to direct it to the proteasome for degradation. They upregulated UHRF-2 and enhanced the degradation of the inclusion bodies, which was neuroprotective in their cell model. This also found this to be true with the inclusion bodies in two other neurological diseases, DRPLA and ataxin-1.

As Dr. Finkbeiner said at a Hereditary Disease Foundation workshop, there are changes in the cell caused by HD which are pathological, changes which are compensatory, and changes which are neither, and it is important to know which is which if we are to identify targets for treatments.

The two teams would seem to have diametrically opposed approaches since Dr. Iwata's team is targeting the aggregates and Dr. Finkbeiner's team views them as neuroprotective. However, it may be that the two research studies are reconcilable in that dissolving the aggregates or preventing aggregation would increase toxicity, but enhancing the ability of the UPS to actually degrade the inclusion bodies and clear the protein away could be an important treatment.

Basic research continues to be important for identifying good targets for treatment. Additional research on the UPS to degrading the HD protein in the cell nucleus should delineate a potentially rich path for therapeutic development.

References

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