Cellular mechanisms underlying detoxification of mutant Huntingtin

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USA

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Research Abstract
? DESCRIPTION (provided by applicant): Huntington's disease is a genetic neurodegenerative disorder caused by expansion of a polyglutamine repeat region in the Huntingtin protein. A paradox of Huntington's Disease is that mutant Huntingtin protein is ubiquitously expressed, but only a subset of central neurons are killed in this disease. That is, some cell types are able to tolerate mutant Huntingtin (mHtt) expression without significant toxicity. The proposed studies

are designed to elucidate the molecular mechanisms by which cells process and remove aggregated mHtt, allowing them to survive. It is generally accepted that misfolded proteins are first held by small heat shock proteins to be refolded, and directed to the ubiquitin-proteasome system (UPS) if they cannot be refolded. When the UPS system is overwhelmed, misfolded proteins are then believed to be retargeted to large protein aggregates (inclusion bodies). However, in this model the role of small fibrillar aggregates, which are now widely believed to be the toxic species of aggregate, is unclear. Previous imaging studies have overwhelmingly focused on inclusion bodies, partly because imaging technologies that could detect small aggregates were not widely available. Using S. cerevisiae, we are able to see both small aggregates and inclusions in the same cell. One model to explain how cells tolerate large amounts of misfolded mHtt would be that small aggregates, produced when the UPS is overwhelmed, join inclusion bodies that are then degraded by autophagy. The proposed studies are designed to test this model. While attention has shifted recently to small aggregate species as the likely cause of most cellular damage, imaging studies of SAS are uncommon. Our first goal is to use advanced imaging and analysis to track small aggregates with respect to the inclusion body, proteasome, and phagocytic compartments, using a genetically tractable system. Second, there is evidence to indicate that the conserved small heat shock protein Hsp42p facilitates mHtt aggregate removal. It has been suggestubiuthat the mammalian sHSP HspB8 acts with Hsp70, BAG3 and microtubule-associated protein 1 light chain 3 (LC3) in promoting autophagy of inclusion bodies. Our second aim is to test the hypothesis that Hsp42p directs inclusion bodies to autophagosomes, a novel function for small heat shock proteins. This work will allow us to define the dynamic behavior of small aggregate species, and develop new techniques to examine inclusion body recycling, using methods that can be used to identify specific molecular deficits in strains known to modulate mHtt processing. Critically, this pilot project will facilitate the development of the PI through mentorship and will support the establishment of an active lab that promotes research training and scientific collaboration.

Further information available at:

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