Published in final edited form as:

Mov Disord. 2017 December ; 32(12): 1686. doi:10.1002/mds.27226.

Polyglutamine Inclusion Body Toxicity

Roger L. Albin, MD

Neurology Service & GRECC, VAAHS, Ann Arbor, MI, 48105, USA

Dept. of Neurology, University of Michigan, Ann Arbor, MI, 48109, USA

Proteinaceous inclusion bodies (IBs) are common features of neurodegenerative proteinopathies, and their role(s) in pathogenesis are frequently debated. This is true for Huntington disease (HD), which exhibits both intranuclear and cytoplasmic IBs composed primarily of mutant protein. The initial recognition of IBs in HD prompted speculation that they drove neurodegeneration. An alternative explanation, supported by sophisticated experimental work and correlative striatal pathologic studies, was that IBs represent protective “sinks” sequestering toxic soluble protein species.^{1,2} Bauerlein et al. report high resolution analysis of intracellular polyglutamine (polyQ) containing inclusion bodies.³ Technical advances in cryo-electron tomography allow remarkably resolute visualization of subcellular structures *in situ*, permitting inferences about physiologic roles, or, as in this case, pathologic effects, of specific structures.

Bauerlein et al. visualized IBs in cells transfected with expanded polyQ exon 1 huntingtin (htt) constructs. IBs consisted of amyloid-like fibrils apparently interacting with cellular endomembranes, particularly endoplasmic reticulum (ER) membranes. Bauerlein et al. present interesting data suggesting that cytoplasmic IBs exert deleterious effects on ER function, consistent with prior suggestions that disrupted ER function is a contributing feature to neurodegeneration in HD.

There are limitations of this technically impressive and visually beautiful work. These are results from over-expression in *in vitro* cell models. While some data derived from cultured neurons, much was obtained in non-neuronal HeLa cells. The constructs used did not produce full length htt. Further work in more realistic models will be needed to extend these observations.

It's important to see this work in broader context. There are several well supported potential mechanisms of neurodegeneration secondary to expanded polyQ htt. Both gain of function toxicities and haploinsufficiency effects may play roles in neurodegeneration. Transcriptional dysregulation, axonal transport defects, mitochondrial dysfunction, aberrant intracellular calcium homeostasis, RNA toxicity, and excitotoxicity, among others, have credible experimental support. This suggests that expanded repeat polyQ htt has pleiotropic

Address correspondence to: Roger L. Albin, MD, 5023 BSRB, 109 Zina Pitcher Place, Ann Arbor, MI, 48109-2200, USA, (ph) 734-764-1347, (fax) 734-763-7686, ralbin@umich.edu.

Bauerlein FJB, Saha I, Mishra A, et al. In Situ Architecture and Cellular Interactions of PolyQ Inclusions. *Cell* 2017;171:171-187.

Author Role: RLA is responsible for all content.

neurotoxic effects, including via soluble protein species. It is plausible that HD IBs act both as protective sinks and have toxic effects.⁴

Some of the Bauerlein et al. data are consistent with this last suggestion. They report that nuclear IBs were not associated with endomembranes. Prior experimental data indicates that nuclear localization of expanded polyQ htt is important in neurodegeneration. It is plausible that nuclear IBs are protective while some cytoplasmic IBs cause ER dysfunction.

The more we learn about the biology of expanded polyQ htt, the more complex the pathogenesis of HD seems.

Acknowledgments

Financial Disclosures: Supported by NIH-NINDS R21 NS088302; P50 NS091856. RLA receives honoraria for DSMB Service for ICON (LEGATO-HD; BMS CN012-002) and IONIS (IONIS-HTTRX). RLA serves on the Editorial Boards of Neurology, Annals of Neurology, Experimental Neurology, and Neurobiology of Disease.

References

1. Arrasate M, Mitra S, Schweitzer ES, Segal MR, Finkbeiner S. Inclusion body formation reduces levels of mutant huntingtin and the risk of neuronal death. *Nature*. 2004; 431:805–810. [PubMed: 15483602]
2. Kuemmerle S, Gutekunst CA, Klein AM, et al. Huntington aggregates may not predict neuronal death in Huntington's disease. *Ann Neurol*. 1999; 46:842–849. [PubMed: 10589536]
3. Bäuerlein FJB, Saha I, Mishra A, et al. In Situ Architecture and Cellular Interactions of PolyQ Inclusions. *Cell*. 2017; 171:179–187. [PubMed: 28890085]
4. Tallaksen-Greene SJ, Ordway JM, et al. Hprt(CAG)146 mice: age of onset of behavioral abnormalities, time course of neuronal intranuclear inclusion accumulation, neurotransmitter marker alterations, mitochondrial function markers, and susceptibility to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. *J Comp Neurol*. 2003; 465:205–219. [PubMed: 12949782]