Polyglutamine Inclusion Body Toxicity

Bäuerlein FJB, Saha I, Mishra A, et al. In situ architecture and cellular interactions of PolyQ inclusions. Cell 2017;171:171-187.

Proteinaceous inclusion bodies (IBs) are common features of neurodegenerative proteinopathies, and their roles 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] Bäuerlein and colleagues[3] report high-resolution analysis of intracellular polyglutamine (polyQ) containing inclusion bodies. 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, the pathologic effects of specific structures.

Bäuerlein and colleagues 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. Bäuerlein and colleagues 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 overexpression in the in vitro cell models. Although some data derived from cultured neurons, much was obtained in nonneuronal 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 is important to see this work in a 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 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 data from Bäuerlein and colleagues 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, whereas 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.

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