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Protein aggregation and neurodegeneration

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In 1997 Carrell and Lomas put forth the concept that many disorders, which appeared to be unlinked, arose from the same general mechanism that involved the abnormal unfolding and aggregation of various underlying proteins [1]. The flux of proteins through pathways for formation of amyloid-like aggregates was proposed to be the mechanism for proteotoxicity. However, whether formation of SDS-resistant amyloid-like aggregates is causative or protective in these protein conformational disorders remains a topic of intense debate [2].

A number of these protein conformational disorders are neurodegenerative diseases such as Alzheimer's Disease, Parkinson's Disease, and polyglutamine repeat diseases. Although little is clearly understood about the toxic species in such neurodegenerative diseases, extensive studies have been carried out to understand the stages of aggregation within the cell. The disease associated protein in these disorders undergoes a conversion from a natively folded, soluble monomer into an assembly of ordered amyloid-like aggregates (Fig. 1). A key step in this pathway is the nucleation of β -sheet rich species. After the protein has passed this thermodynamically unfavorable step, assembly occurs much more easily and may result in an amyloid-like fibril. Recent evidence suggests that a small oligomeric species, which could be part of an intermediate or off-pathway assembly step, may be the toxic culprit in some aggregation related diseases, although this varies depending on the disease associated protein. Therefore, one mechanism of protection against proteotoxicity in certain protein conformational disorders may require the cell to suppress the switching from native disease proteins to assembled forms, because intermediates of such pathways kill cells.

Interactions between arrays of intracellular factors also affect proteotoxicity via both positive and negative influences on the cell's ability to buffer potentially toxic protein species [3–6]. Indeed, molecular chaperones protect cells from proteotoxicity by suppressing the initial oligomerization of disease proteins, promoting their degradation; they also stimulate the conversion of amyloid assembly intermediates into benign aggregates [7–9]. Thus, the cell must decide the fate of the misfolded protein either towards promotion of a large benign aggregate assembly or targeting for degradation.

Researchers have developed a wide array of both *in vivo* and *in vitro* techniques to study how cells partition misfolded proteins and handle intracellular aggregates, each of which has

its own strengths. For example, purification and study of aggregation prone disease related proteins *in vitro* allows for detailed analysis of structural folding dynamics. Alternatively, utilizing yeast, fly, and worm model systems allows for detailed genetic manipulation to analyze proteostatic networks among many other things. Additionally, mammalian studies in mice or cell culture can be exploited to examine disease relevant situations such as treatments for various neurodegenerative disorders. This issue of Methods encompasses a variety of techniques and model systems which give investigators a powerful toolbox applicable to the study of protein aggregation and neurodegeneration.

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Fig. 1.

Protein folding pathway. Although proteins have a normal or native fold, they also can be partitioned into several other conformational fates. These include misfolding or abnormal folding, accumulating as an ordered or disordered aggregated species, and degradation. Sometimes a protein comes into contact with another surface that influences how it folds. This interaction could be called nucleation since the newly “templated” monomer can now influence even more monomers to adopt a similar fold and may result in a possible small oligomeric assembly or an amyloidogenic aggregate. Further packaging may occur in order for the amyloidogenic aggregates to be incorporated into inclusion bodies or amyloid fibrils, but whether these large aggregates or the small oligomeric species are toxic remains a point of controversy.