

## Protein Aggregation in Neurodegenerative Disorders: A Cause or Consequence?

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### Introduction

Proteins are three dimensional indispensable complex macromolecules of organisms which play essential role in every aspect of biological functions. Notably, all the proteins must be folded precisely to perform such diverse cellular functions. Three dimensional structures are primarily determined by amino acid sequence of polypeptide chain and several other associated factors [1]. However, there are many circumstances when newly synthesized or denatured proteins are not folded correctly and in such cases they exhibit strong tendency to aggregate [2]. Heat shock proteins or chaperones play a vital role in folding/re-folding of protein, and therefore, prevent aggregation and accumulation of abnormally folded proteins [3]. In this context it is important to note that chaperones have limited protein folding and re-folding capacity which become increasingly noticeable during stress or disease conditions. Protein aggregates has toxic effects when accumulated above a threshold level [2]. In addition to stresses, mutations play determinative role in protein aggregation and dramatically alter solubility, stability, and aggregation tendency of proteins [4]. Nervous systems are especially sensitive to such changes and accumulation of protein aggregates may lead to progressive impairment and loss of neuronal cells as observed in protein folding diseases such as Huntington's diseases (HD), Alzheimer's disease (AD), Parkinson's disease (PD) etc. [5].

### Protein Aggregation and Cellular Toxicity

Interestingly, when Alois Alzheimer first observed that post-mortem brains of a severely demented patients contained proteinaceous amyloid plaques, he was puzzled whether accumulation of these proteinaceous substances caused or resulted from neurodegeneration. Even more than a century later, this question is being vigorously investigated but not conclusively answered. Moreover, molecular mechanisms of protein aggregations and pathogenesis of neurodegenerative diseases are not fully understood. However, possibility that protein aggregation could be the root cause of neurodegeneration gained attention with the report which demonstrates that a gene encoding a precursor of the amyloid- $\beta$  protein ( $A\beta$ ) is linked to autosomal dominant familial form of AD [6].  $A\beta$  is a 4-kDa peptide which comprises the least soluble, fibrillar component of AD amyloid plaques [7]. It was postulated that protein aggregation above threshold level triggers the cascade of events that result in neurodegeneration and manifestation of disease phenotypes [8]. This "amyloid hypothesis" has become apparent in view of the fact that most neurodegenerative diseases could be characterized by accumulation of protein aggregates, albeit of varying composition [9]. In this context it is also interesting to note that protein aggregation appears to be a complex multi-step process with several potential intermediate species, including oligomeric and protofibrillar forms [10]. It is not clear whether particular molecular species i.e. monomers, oligomers, protofibrils or any specific forms of fibrils is responsible for toxicity.

Interestingly, several studies propose that formation of protein inclusion bodies as found in HD could be separated from cellular toxicity, and might be correlated with a cellular protective response [11]. How

could this apparent contradiction be resolved or justified that the process of protein aggregation might be linked with neurotoxicity, but that the inclusion bodies may be protective? There are however increasing but still indirect evidences which suggest that inclusion bodies might represent an end-stage manifestation of a multistep protein aggregation process [11,12]. It has been proposed that early events before the formation of inclusion bodies might cause toxicity. Possible factors may include abnormal monomers of the disease proteins or small assemblies of abnormal aggregates termed as oligomers or protofibrils. In this context it is also interesting to note that presence of inclusion bodies sometime poorly correlates with other cellular markers of neurodegeneration [13]. This lack of correlation is most apparent in cases of polyglutamine disorders. For instance, in HD, inclusion bodies are present in the cells of the striatum which undergoes massive degeneration, but are more abundant in the cerebral cortex, which undergoes only moderate degeneration [14]. Expression of proteins that contain expanded polyglutamine stretches in neuronal cell culture model leads to robust cell death, making this a decent model to investigate the toxic effect of mutant poly(Q) protein. Initial studies suggest that inclusion bodies have little correlation with neuronal toxicity, although the circumstances might not have been representative of *in vivo* condition [15]. It has been proposed that the inherent tendency of proteins to form aggregates has made it necessary for cells to develop several defence strategies against misfolded or abnormal proteins. Some of such defence strategies include folding machinery mediated by molecular chaperones, proteasomal system and autophagy [11,16]. It has also been proposed that when abnormal and aggregated proteins cannot be refolded or degraded by proteasomal machinery or chaperone mediated autophagy; cells sequester the aggregates by microtubule-mediated transport system and collect them at a single cytoplasmic site through an alternative line of defence. Such phenomenon leads to formation of large inclusion bodies which are easily visible by light microscope and known as aggresomes. Interestingly, the Lewy bodies of PD are strikingly similar to aggresomes [17].

### Conclusion and Future Prospects

Importantly, irrespective of the nature of the toxic species, it is more crucial to determine the molecular mechanisms of cellular toxicity. Although several hypotheses have been proposed, however, protein aggregate mediated impairment of cellular defence systems

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and reduction in global transcriptional efficiency appears to be the leading cause of neurotoxicity. Therefore, detection of the onset of the neurodegenerative-disease process before full phenotypic manifestation is a critical aspect of disease management. If the pre-symptomatic neurodegenerative disease could be established and treated, the occurrence of symptomatic disease could be greatly reduced. Since majority of the neurodegenerative diseases are genetically complex (HD is the exception), pre-symptomatic diagnosis requires identification of peripheral markers for neurodegeneration that reacts earlier and is more reliable than the traditional symptoms, or that the progression of protein aggregation is observable and measurable in brain. Once early protein aggregation has been detected, the patient could be treated with disease-modifying drugs to reduce the amount of aggregates in target tissues. Therefore, it is essential to gain a better understanding of the exact molecular composition, reactivity and molecular structure of abnormally folded monomers, oligomers and protein aggregates. Since most of the information on protein aggregation is based on data obtained *in vitro*, an important task for future studies would be to dissect these pathways *in vivo*. In addition, it is crucial to upsurge our understanding of the initiating events which lead to formation of the abnormal protein conformation and aggregation. Characterization of such initial events could be extremely important to design novel therapeutic strategies. Subsequent identification of molecule(s) which reduces protein aggregation i.e. reducing production of the aggregating protein or by stimulating the aggregate clearance pathway could greatly help in management of neurodegenerative disorders. Taken together, it is difficult to establish a precise relationship between protein aggregation and neurodegeneration until we develop a better and holistic understanding of the underlying signalling events and discover/verify some potent modifier molecules.

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