

## Editorial

# Protein Misfolding in Neurodegenerative Diseases: The Key Pending Questions

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## EDITORIAL

Neurodegenerative diseases are chronic and often fatal illnesses that affect the most precious qualities of human beings. This group of disorders include highly prevalent diseases such as Alzheimer's and Parkinson's, and other rarer as Huntington's disease, spinocerebellar ataxia, prion diseases (also called transmissible spongiform encephalopathies), and amyotrophic lateral sclerosis. Despite the diversity in clinical manifestation, neurodegenerative diseases share many common features including their relationship to aging, the progressive and chronic nature of the disease, the extensive, but localized loss of neurons and synaptic abnormalities and the presence of cerebral deposits of misfolded protein aggregates. Research over the past 20 years has provided compelling evidence for a key role of these aggregates as the culprits of neurodegeneration [1,2]. Each neurodegenerative disease is associated with abnormalities in the folding, leading to formation of oligomers and large aggregates composed of a different protein. In this article, I outline the main pending questions related to the involvement of misfolded protein aggregates in neurodegenerative diseases.

## Are misfolded aggregates the cause of neurodegeneration?

Despite compelling evidence from genetic, biochemical and neuropathological analysis as well as studies with animal models, it still remains not completely proven that accumulation of misfolded protein aggregates is the underlying cause of the disease [1-3]. It is likely that the definitive proof will only be obtained if the disease can be successfully treated or prevented by elimination of misfolded aggregates.

## What is the identity and structure of the toxic form of misfolded aggregates?

The process of protein misfolding and aggregation results in the formation of a continuum of particles of different size and structure, ranging from dimers to very large fibrils [1-5]. The majority of the evidence points that small, soluble oligomers are the most neurotoxic species in the brain [4-6]. However, it is likely that many different aggregates may be toxic, perhaps by distinct mechanisms. Moreover, it seems clear that the various

particles are in a dynamic equilibrium among each other, further complicating the study of their specific properties. The heterogeneity, interconversion, insolubility and non-crystalline nature of misfolded aggregates impose enormous complications for elucidation of the atomic-resolution structure of these molecules [7-10]. Nevertheless, much progress has been done in recent years, especially using short peptide models of protein aggregates [9,10].

## How misfolded aggregates induce neuronal damage?

It was initially thought that neuronal apoptosis was the most important problem in neurodegeneration, however recent evidence from different diseases, suggest that extensive neuronal death may not be the initial cause of the disease [11-13]. Indeed, clinical symptoms have been clearly described before significant neuronal loss and a better temporal and topographic correlation is found with synaptic dysfunction. Although the mechanism of neurotoxicity is a topic extensively studied and many different hypotheses have been proposed, it is still unclear which of the different models operates in vivo in the human brain. Some of the pathways proposed include (for reviews, see [14-18]) : (i) activation of signal transduction pathways leading to neuronal dysfunction; (ii) recruitment of cellular factors essential for neuronal functioning; (iii) membrane disruption and depolarization mediated by pore formation; (iv) impairment of the protein homeostasis machinery in the cell; (v) extensive oxidative and endoplasmic reticulum stress; (vi) induction of mitochondrial dysfunction; (vii) triggering a chronic inflammatory reaction in the brain.

## What is the role of the cellular defense mechanisms against accumulation of misfolded aggregates?

The net accumulation of protein aggregates depend upon the rates of misfolding and aggregation as well as the rate of clearance of misfolded aggregates. To combat the formation of misfolded aggregates, cells have developed complex and complementary pathways aiming to maintain protein homeostasis. These protective pathways include the unfolded protein response, the ubiquitin protease system, autophagy and the encapsulation of the damaged proteins in aggresomes [19,20]. Comparatively

much more effort has been devoted to understand how proteins misfold and aggregate as well as the cellular, genetic and environmental factors implicated, than in elucidating the role of the natural defense mechanisms. It is likely that better understanding of these processes may lead to novel strategies for treatment based on boosting the endogenous mechanisms to remove misfolded aggregates.

### **What is the mechanism responsible for the selective neuronal vulnerability of distinct misfolded aggregates?**

One of the most puzzling aspects of neurodegenerative diseases is that diverse disorders consist on the accumulation of misfolded aggregates in different areas of the brain, which affect selective populations of neurons [21,22]. The fact that many of these proteins express ubiquitously throughout the brain makes difficult to understand the selective neuronal vulnerability and suggest that expression of other proteins and/or specific changes on the milieu of different neurons may be implicated. Although several hypotheses have been proposed to explain selective neuronal vulnerability in neurodegenerative disease [21-25], much more research is needed to address this important topic, which likely will contribute to the development of therapeutic interventions for neurodegenerative diseases.

### **Do misfolded aggregates spread in a prion-like infectious manner?**

Among neurodegenerative diseases, prion disorders are unique because the pathology can be naturally and experimentally transmitted between individuals. Strikingly, the infectious agent responsible for prion diseases (termed prion) is composed exclusively by the misfolded and aggregated form of the prion protein [26,27]. Prion replication depend on the auto-catalytic conversion of the normal prion protein catalyzed by small amounts of the misfolded and infectious form of the prion protein [27,28]. The conversion of the normal into the abnormal prion protein follows a seeding-nucleation mechanism, in which oligomers of the misfolded protein bind, induce the misfolding and integrate the normal protein into the growing aggregates [4,29]. Importantly, formation of misfolded aggregates in all other neurodegenerative diseases follow the same seeding-nucleation mechanism, suggesting their potential to propagate as a prion [28,29]. Remarkably, during the last 5 years a series of groundbreaking reports have shown that the protein misfolding and aggregation, characteristic of the most prevalent neurodegenerative diseases, can be experimentally transmitted in animal models through a prion-like principle (for reviews, see [28,30-33]). These studies have produced a tremendous paradigmatic change in our understanding of the molecular bases of neurodegenerative diseases. However, it remains to be study whether prion-like spreading and transmission of misfolded aggregates indeed occur under natural conditions in humans. It is likely that, in the same manner as in prion diseases, the prion-like principle operates in neurodegenerative disorders much more frequently in the cellular and tissue spreading of misfolded aggregates within an individual, than in the rare cases of inter-individual transmission.

### **Are misfolded aggregates a good target for therapeutic intervention?**

Despite dramatic progress in understanding the pathogenesis of neurodegenerative diseases, none of these disorders can yet be successfully treated. If protein misfolding and aggregation is a central event in the pathogenesis of these diseases, a therapy directed to the cause of the illness should aim to prevent or even reverse the formation of misfolded aggregates. Several approaches have been proposed to target the process of protein misfolding and aggregation (for reviews, see [1,3,10,34,35]) : 1) decrease of the expression of the protein implicated in misfolding and aggregation; 2) stabilization of the native protein conformation; 3) inhibition and reversal of protein conformational changes leading to the formation of misfolded aggregates; 4) increase the biological clearance of the misfolded protein; 5) prevent or correct the downstream deleterious effects of misfolded protein aggregates. All these targets have been studied extensively and for most of them good results have been obtained in animal models of the various diseases. However, most of the few drugs tried in human clinical trials have consistently failed in producing benefits to the patients. It is very likely that the main reason for these failures is that preventing or even reverting the accumulation of misfolded aggregates in symptomatic patients is probably too late to produce clinical benefit [36]. For these diseases, at the time in which patients exhibit clear symptoms of the disease and they can be properly diagnosed, the brain is largely destroyed.

### **Is the sensitive and specific detection of misfolded aggregates a promising strategy for early disease diagnosis?**

As stated above, pre-symptomatic diagnosis of neurodegenerative diseases is a high priority to enable efficient therapeutic intervention. Traditionally, diagnosis of these diseases is achieved after clear clinical symptoms are evident and even then definitive diagnosis is only accomplished after postmortem examination of the brain [37,38]. To attempt early and non-invasive diagnosis of neurodegenerative diseases, many laboratories have been investigating the use of diverse neuroimaging approaches and the identification of disease-specific biomarkers [38-40]. Although, these strategies may well achieve the goal, it seems that detection of misfolded aggregates is the best option, because of the tight involvement of these structures in the disease pathogenesis. The process of formation and accumulation of misfolded aggregates begins years or even decades before the onset of clinical symptoms [38,41,42] and several lines of evidence suggest that soluble misfolded oligomers might be circulating in biological fluids (blood, cerebrospinal fluid, etc) [43-47]. In recent years there have been several reports describing various approaches for imaging-based detection of protein aggregates as well as for biochemical detection of these molecules in fluids [39,40,48]. These recent developments coupled with the large effort from the pharmaceutical industry to come out with efficient disease-modifying strategies raises hope for the ultimate goal of eradicating neurodegenerative diseases by combining a highly sensitive early diagnosis with an efficient and safe therapeutic strategy.

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