Review

Protein misfolding and disease: the case of prion disorders

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Abstract. Recent findings strongly support the hypothesis that diverse human disorders, including the most common neurodegenerative diseases, arise from misfolding and aggregation of an underlying protein. Despite the good evidence for the involvement of protein misfolding in disease pathogenesis, the mechanism by which protein conformational changes participate in the disease is still unclear. Among the best-studied diseases of this group are the transmissible spongiform encephalopathies or prion-related disorders, in which misfolding of the normal prion protein plays a key role in the disease. In this article we review recent data on the link between prion protein misfolding and the pathogenesis of spongiform encephalopathies.

Key words. Protein conformational disorders; prion protein misfolding; transmissible spongiform encephalopathies; neuronal apoptosis; brain inflammation; prion protein function.

Introduction

Analysis of the neuropathological characteristics of several degenerative diseases has revealed common features underlying the mechanism of disease initiation and progression. In the last few years, protein misfolding has been proposed to be a central aspect of diverse diseases which are now classified as protein conformational disorders (PCDs) [1, 2]. This group includes transmissible spongiform encephalopathies (TSEs), Alzheimer disease, diabetes type 2, Huntington disease, serpin-deficiency disorders, Parkinson disease, amyloid polyneuropathy, haemodialysis-related amyloidosis and several others (table 1). Despite the very different clinical manifestations of diverse PCDs, there are many similarities at the molecular level. In the cases of PCDs in which the protein involved is known, the pathological conformation is rich in \( \beta \)-sheet structure and shows a capacity to oligomerize or aggregate due to protein stabilization by intermolecular \( \beta \)-sheet interactions [2]. This leads to accumulation of different forms of protein aggregates in diverse tissues of affected individuals (table 1). Among the PCDs that have been extensively studied in terms of the involvement of protein misfolding in the pathogenesis of the disease is TSE, or prion disease.

TSEs are rare fatal neurodegenerative diseases of humans and other animals [3, 4]. Primary symptoms include progressive dementia and ataxia [5]. The hallmark pathological features of TSEs are spongiform degeneration of the brain, accompanied by extensive astrogliosis, and accumulation of the abnormal, protease-resistant prion protein (PrP) isoform in the central nervous system, which sometimes forms amyloid-like plaques [3, 6]. TSEs in humans can be divided in three groups: familial, sporadic and infectious. Human familial TSEs are all associated with different mutations in the PrP gene, and include some forms of Creutzfeldt-Jakob disease (CJD), Gertmann-Straussler-Sheinker (GSS) syndrome and fa-
tal familial insomnia (FFI) [7]. Sporadic CJD has not been associated with any known mutation and occurs worldwide with an incidence of 0.5–1.5 new cases per 1 million people each year [8]. Infectious TSE diseases include kuru, which was propagated by ritualistic cannibalism, and iatrogenic CJD, which is spread by tissue transplantation, contamination of surgical tools or inoculation with materials derived from CJD-infected tissues [4]. New variant CJD (vCJD) is a novel infectious disease which was first described in 1996 [9]. In animals, the most common disease is scrapie in sheep and goats, and bovine spongiform encephalopathy (BSE) or ‘mad cow disease’ in cattle [3]. There is strong evidence linking the appearance of vCJD in humans to exposure to the BSE agent, most possibly through dietary contamination with BSE tissue [10, 11].

Despite the fact that TSEs are relatively rare diseases, they have gained significant attention from the scientific community and society in general [12], affecting medical, agricultural, economic and political issues in Europe. Although an estimated 750,000 BSE-infected cattle were eaten by humans between about 1980 and 1996, it is impossible to make any well-founded predictions about the future number of vCJD cases, because insufficient information is currently available regarding the incubation time and the actual level of exposure to contaminated material [13].

In the present article, we review the putative mechanism by which protein misfolding and aggregation is associated with the tissue damage and organ dysfunction using TSEs as a model. The major aim is to put together findings related to the cellular mechanism by which misfolding of the PrP is associated with neurodegeneration in TSEs. Although we describe briefly some aspects of the structure of the PrP, the mechanism of prion replication and the nature of the infectious agent, more in-depth reviews about these aspects can be found elsewhere [3, 4, 12, 14–17].

### Disease propagation by replication of PrP misfolding

As mentioned above, a hallmark feature of TSE is accumulation in the brain of affected individuals of PrPSc, a misfolded form of normal prion protein. Human PrP is the product of a single gene which leads to synthesis of a protein of 253 amino acids containing five octapeptide repeats near the amino-terminal, two glycosylated sites and one disulfide bridge (fig. 1A). In addition, a glycosylphosphatidylinositol anchor (GPI) attaches the protein to the outer surface of the cell membrane [18]. The PrP gene is constitutively expressed in the brain and other tissues of healthy people and animals. No sequence or post-translational differences have been detected between the normal host cell surface PrP, termed PrPC, and the pathological PrPSc isoform [4]. The conversion of PrPC into PrPSc involves a conformational change whereby the α-helical content diminishes and the amount of β sheet increases [19] (fig. 1B). This structural transition is accompanied by profound changes in the biochemical properties of the protein: PrPC is soluble in nondenaturating detergents, whereas PrPSc is insoluble and forms aggregates in infected brain parenchyma. PrPC is readily digested by proteases, while PrPSc is partially resistant. However, even though PrPSc has a marked tendency to aggregate in vitro, forming amyloid prion rods, accumulation of amyloid plaques in the brain is observed only in a small percentage of TSE cases [4].

### Table 1. Common features of some neurodegenerative diseases that have been classified in the group of protein conformational disorders.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Protein involved</th>
<th>Type of aggregates</th>
<th>Brain inflammation</th>
<th>Neuronal apoptosis</th>
<th>Proposed function normal protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSEs</td>
<td>Prion protein</td>
<td>oligomers/plaques</td>
<td>extensive</td>
<td>extensive</td>
<td>signal transduction, antioxidant, copper binding</td>
</tr>
<tr>
<td>Alzheimer</td>
<td>amyloid-β</td>
<td>amyloid plaques</td>
<td>extensive</td>
<td>sporadic</td>
<td>neurite outgrowth, synaptic vesicle transport</td>
</tr>
<tr>
<td>Parkinson</td>
<td>α-synuclein</td>
<td>Lewy bodies</td>
<td>sporadic</td>
<td>extensive</td>
<td>regulation of membrane stability/or turnover</td>
</tr>
<tr>
<td>Huntington</td>
<td>Huntington</td>
<td>nuclear inclusions</td>
<td>N.D.</td>
<td>extensive</td>
<td>transcriptional regulation</td>
</tr>
</tbody>
</table>

N.D., not well determined in human samples.