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Animal models for prion-like diseases

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ABSTRACT

Prion diseases or Transmissible Spongiform Encephalopathies (TSEs) are a group of fatal neurodegenerative disorders affecting several mammalian species being Creutzfeldt-Jacob Disease (CJD) the most representative in human beings, scrapie in ovine, Bovine Spongiform Encephalopathy (BSE) in bovine and Chronic Wasting Disease (CWD) in cervids. As stated by the "protein-only hypothesis", the causal agent of TSEs is a self-propagating aberrant form of the prion protein (PrP) that through a misfolding event acquires a β-sheet rich conformation known as PrP^{Sc} (from scrapie). This isoform is neurotoxic, aggregation prone and induces misfolding of native cellular PrP. Compelling evidence indicates that disease-specific protein misfolding in amyloid deposits could be shared by other disorders showing aberrant protein aggregates such as Alzheimer's Disease (AD), Parkinson's Disease (PD), Amyotrophic lateral sclerosis (ALS) and systemic Amyloid A amyloidosis (AA amyloidosis). Evidences of shared mechanisms of the proteins related to each disease with prions will be reviewed through the available *in vivo* models. Taking prion research as reference, typical prion-like features such as seeding and propagation ability, neurotoxic species causing disease, infectivity, transmission barrier and strain evidences will be analyzed for other protein-related diseases. Thus, prion-like features of amyloid β peptide and tau present in AD, α-synuclein in PD, SOD-1, TDP-43 and others in ALS and serum α-amyloid (SAA) in systemic AA amyloidosis will be reviewed through models available for each disease.

1. Introduction

In the last few decades, the alarming increase in age-related neurodegenerative disorders associated to the increase in life expectancy has led to great effort in research and the discovery of new pathogenic mechanisms behind these diseases.

The intensive research has pointed out that an important group of the age-related neurological disorders are characterized by the presence of aggregates of a determined misfolded protein in specific regions of the nervous system. Thus, Alzheimer's Disease (AD) is characterized by accumulation of Amyloid beta (Aβ) peptide and tau aggregates (Nussbaum et al., 2013), the latter also appearing in many tauopathies as Frontotemporal Dementia (FTLD) (Gasparini et al., 2007). Parkinson's Disease (PD) with α-synuclein aggregates (Olanow and Brundin, 2013) and Amyotrophic Lateral Sclerosis (ALS) showing Transactive Response DNA Binding Protein 43 (TDP-43) and Cu-Zn Superoxide Dismutase 1 (SOD-1) aggregates (Polymenidou and Cleveland, 2011). And Transmissible Spongiform Encephalopathies (TSEs), as Creutzfeldt-Jacob Disease (CJD) in humans, scrapie in sheep or Bovine Spongiform Encephalopathy (BSE) in cattle are caused by the prion protein (PrP) (Aguzzi and Calella, 2009). Since the proteins involved in each disorder are different and the affected areas and the resulting clinical signs as well, all were thought to have unrelated pathogenic mechanisms. However, since the 1980s some similarities were already observed and pointed out by different researchers at the very beginning of detailed molecular studies of those diseases. Although clear differences between AD and CJD such as transmissibility between individuals dismissed a common etiology, the discovery of common features as the biophysical similarities between amyloid deposits pointed to some resemblance or possible relation between both diseases (Brown et al., 1982; Prusiner, 1984).

Apart from the age-related neurological disorders, systemic amyloidosis is also part of the growing family of protein misfolding-related diseases possibly sharing prion-like mechanisms. Among the many systemic amyloidoses caused by diverse serum precursor proteins, reactive amyloid A (AA) amyloidosis (Murakami et al., 2014) is one of the better characterized and will be used as example

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to analyze prion-like features that could be common to all the systemic amyloidoses in addition to the above mentioned age-related neurological disorders.

Together with a much better understanding of the molecular mechanisms of most of the above-mentioned disorders, more and more similarities are arising. It seems clear now that disease-specific protein misfolding and aggregation in amyloid deposits are not the only commonality shared. For TSEs, the protein-only hypothesis proposed over two decades ago by Stanley Prusiner states that the self-templated misfolding of PrP into an infectious and neurotoxic isoform known as prion is the etiologic agent (Diener et al., 1982). Much more recent research performed on the other above mentioned disorders has shown that the self-templating or seeding ability of the proteins involved in each disease may be a shared primary pathogenic mechanism that leads to the amyloid plaques characteristic of all of them (reviewed in Kraus et al., 2013). Moreover, the cell-to-cell transmission or propagation of protein aggregates, well known for prions, has been also proved for Aβ, tau, α-synuclein, SOD-1 and TDP-43 (Clavaguera et al., 2009; Grad et al., 2011; Nath et al., 2012; Nonaka et al., 2013). Another important shared concept derived from recent research is the fact that the cognitive decline occurs uncoupled from the amyloid load. Thus, synaptic loss and neurodegeneration seems to be linked to oligomeric species formed early in the protein misfolding pathways rather than to the formation of amyloid aggregates. These oligomeric species are thought to be the most neurotoxic forms of the proteins involved in each disorder acting through activation of unknown cellular processes (reviewed in Halliday et al., 2014).

All these features, together with the recent evidences showing characteristics related to TSEs in some of the above mentioned disorders, have led many researchers to use the term "prion-like" to describe all the common facts observed in the protein-misfolding related neurodegenerative disorders and other amyloidoses. Furthermore, the discovery of these shared pathophysiological features enables the grouping of these disorders under the "prion-like disorders" tag and more importantly, allows researchers from traditionally separated areas to join efforts toward the understanding of the still poorly known common mechanisms and to the proposal of common therapies to treat all these fatal diseases.

2. Prion-like disorders. A growing family

Q5 TSEs or prionopathies are a group of rare and fatal neurodegenerative disorders affecting several mammalian species including humans. The best known examples of prion diseases are scrapie in ovines, BSE in bovines, Chronic Wasting Disease (CWD) in cervids, and Creutzfeld-Jacobs disease (CJD), Gerstmann-Straüssler-Scheinker (GSS) and Fatal Familial insomnia (FFI) in humans. All of them are characterized by long incubation periods and spongiform changes in the brain associated with neuronal loss. These clinical features are related to the misfolding of the cellular prion protein (PrP^{C}) into a β-sheet rich infectious, transmissible and aggregation prone isoform known as PrP^{Sc}. The initial misfolding event can start from three different origins: (1) spontaneously, leading to a sporadic prion disease, (2) caused by mutations in the gene coding for the PrP, as seen in inherited or familial forms of prion disease or (3) by acquisition of PrP^{Sc} from other affected individuals of the same or different species, which is known as an infectious prion disease (Aguzzi and Calella, 2009). The highly controversial etiologic agent, now widely accepted to be the PrP^{Sc} or prion according to the protein-only hypothesis proposed by Stanley Prusiner in the 1980s (Diener et al., 1982), brought into the playground a completely new infectious agent that, in the light of recent research on the mentioned protein-related neurodegenerative disorders, seems not to be so unique.

Alzheimer's disease is one of the best examples of a fatal neurodegenerative disorder involving self-templating amyloidogenic proteins as key physiopathological features. AD is the major cause of dementia and the most prevalent age-related neurodegenerative disorder, which also makes it a major public health problem mostly in developed countries due to the increase in the life expectancy of the population. It is characterized by progressive memory loss that eventually progresses to severe cognitive and behavioral decline. It is pathologically distinguished by the presence of extracellular amyloid plaques, intracellular and extracellular neurofibrillary tangles (NFTs) and neuronal loss. The first are mainly composed of Aβ peptide derived from aberrant and heterogeneous processing of Amyloid Precursor Protein (APP) by β and γ-secretases. This generates a heterogeneous population of Aβ peptides (Aβ40 and Aβ42) that form oligomeric complexes and assemble into amyloid plaques (Saraceno et al., 2013). NFTs are also tightly packed protein filaments, composed of hyperphosphorylated tau protein, a microtubule associated protein (MAP) involved in microtubule polymerization (Nussbaum et al., 2013). The presence of two different protein aggregates makes AD a multifaceted pathology with an unclear etiologic agent. However, although it is still highly controversial, the most widely accepted amyloid cascade hypothesis states Aβ as the primary responsible triggering a cascade of events that leads to tau pathology, synaptic dysfunction and neurodegeneration (Walsh et al., 2002). The inherited or familial forms of AD, known as early onset familial AD (FAD), are linked to many different mutations in the APP gene or in the presenilin 1 (PSEN1) or presenilin 2 (PSEN2) genes, which are part of the catalytic activity of the γ-secretase. FAD counts for only 5% of AD cases, the late onset AD (LOAD) being much more common, not associated to mutations in APP or presenilin but occurring sporadically in people over 65 years old and linked to many risk factors as the expression levels of the ε4 allele of the apolipoprotein E (APOE) (Schaeffer et al., 2011; Saraceno et al., 2013). Due to the FAD mutations, always involving Aβ processing, the putative role of tau as primary cause in AD has always received much less attention. Although it is well known that tau alterations leading to paired helical filaments (PHFs) which in AD progress to NFTs, these are also found in a large group of neurodegenerative disorders known as non-Alzheimer tauopathies. It is the case of diseases such as Frontotemporal dementias (FTD) which are associated to a wide variety of tau mutations and where Aβ seems not to be implicated (Nussbaum et al., 2013). The focus on Aβ and the amyloid cascade hypothesis strongly supported by FAD cases and many other experiments allowed the modeling of AD in transgenic animals expressing the mutated APP or presenilins. However, none of them reproduced completely the complex and multifaceted AD pathology, especially the sporadic form of the disease accounting for 95% of the cases. Addition of mutated tau, creating bigenic mouse models, was needed to study the interactions of Aβ and tau. All these constantly improving animal models keep giving invaluable insight into the understanding of this complex pathology, such as the facts that soluble Aβ forms rather than large fibrils correlate with the progression and severity of the disease or that Aβ may interact with tau to accelerate NFT formation (Elder et al., 2010; Schaeffer et al., 2011).

Following AD, Parkinson Disease (PD) ranks second to neurodegenerative disorders prevalence and is characterized by an age-related deterioration of dopaminergic neurons mainly in the substantia nigra. PD is also characterized by aggregation of a misfolded protein, α-synuclein (α-syn), a natively unfolded cytoplasmic protein found mainly in presynaptic terminals but widely expressed in the whole central nervous system (CNS). This protein lies in the core not only of PD but also in some other less common synucleinopathies such as Dementia with Lewy Bodies (DLB),

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