Biochemical and Biophysical Research Communications xxx (2016) 1–12

Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

Prion-like disorders and Transmissible Spongiform Encephalopathies: An overview of the mechanistic features that are shared by the various disease-related misfolded proteins

Hasier Eraña [a], Vanesa Venegas [a], Jorge Moreno [a], Joaquín Castilla [a, b, *]

[a] CIC bioGUNE, Parque Tecnológico de Bizkaia, 48160, Derio, Spain
[b] IKERBASQUE, Basque Foundation for Science, Bilbao, 48011, Bizkaia, Spain

ARTICLE INFO

Article history:
Received 8 July 2016
Received in revised form
4 August 2016
Accepted 29 August 2016
Available online xxx

Keywords:
Prion
Prion-like diseases
Transmissible Spongiform Encephalopathy (TSE)
Alzheimer
Protein misfolding disorders
Prion strain

ABSTRACT

Prion diseases or Transmissible Spongiform Encephalopathies (TSEs) are a group of fatal neurodegenerative disorders affecting several mammalian species. Its causative agent, disease-associated prion protein (PrP^d), is a self-propagating β-sheet rich aberrant conformation of the cellular prion protein (PrP^C) with neurotoxic and aggregation-prone properties, capable of inducing misfolding of PrP^C molecules. PrP^d is the major constituent of prions and, most importantly, is the first known example of a protein with infectious attributes. It has been suggested that similar molecular mechanisms could be shared by other proteins implicated in diseases such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis or systemic amyloidoses. Accordingly, several terms have been proposed to collectively group all these disorders. Through the stringent evaluation of those aspects that characterise TSE-causing prions, in particular propagation and spread, strain variability or transmissibility, we will discuss whether terms such as "prion", "prion-like", "prionoid" or "propagon" can be used when referring to the aetiological agents of the above other disorders. Moreover, it will also be discussed whether the term "infectious", which defines a prion essential trait, is currently misused when referring to the other misfolded proteins.

Contents

* Corresponding author. CIC bioGUNE, Parque tecnológico de Bizkaia, Derio, 48160, Bizkaia, Spain.
E-mail address: castilla@joaquincastilla.com (J. Castilla).

http://dx.doi.org/10.1016/j.bbrc.2016.08.166
0006-291X/

1. Introduction

The notable growth of age-related neurodegenerative disorders linked to increased life expectancy has boosted considerably investigations to determine their pathogenesis. The intensive research during the last two decades has shown that a common feature of all neurodegenerative disorders is the presence of aggregates of misfolded proteins in specific regions of the nervous system. This is the case in Alzheimer's disease (AD), which is characterized by accumulation of Amyloid beta (Aβ) peptides and tau [1], the latter being also a marker for the so-called tauopathies such as Frontotemporal Dementia (FTD) [2]; Parkinson's disease (PD) with α-synuclein aggregates [3]; Amyotrophic Lateral Sclerosis (ALS) showing aggregates of Transactive Response DNA Binding Protein 43 (TDP-43) and Cu-Zn Superoxide Dismutase 1 (SOD-1) [4]; Transmissible Spongiform Encephalopathies (TSEs), e.g., Creutzfeldt-Jacob Disease (CJD) in humans, scrapie in sheep or Bovine Spongiform Encephalopathy in cattle, characterized by prions that, originating from a conformation remodeling of a cellular protein named prion protein (PrP^C), have been the first example of proteinaceous agents with self-perpetuating aggregation and infectious characteristics (see the last section) [5]. Systemic amyloidosis is also part of the growing family of protein misfolding-related diseases. Among the many types of this syndrome - caused by various serum precursor proteins - reactive amyloid A (AA) amyloidosis [6] is one of the best characterized, and will thus serve as example to analyze prion-like features that could be common to all systemic amyloidoses.

The known similarities in the molecular mechanisms of these diseases have led to their grouping under several terms according to their resemblance to prion features. However, the divergent opinions on a single term that would most suitably represent protein misfolding-related diseases have resulted in a multitude of terms including “prion”, “prion-like”, “prion-related”, “propagon” or “prionoid” [7–9]. The preference of the present authors for the term “prion-like” is because not all of the molecular features of prions have been shown to be present in the other protein-misfolded agents, which automatically excludes the term “prion”. Although “prion-related” or “prionoid” could be equally valid, it is our opinion that the term “prion-like” is the most clearly descriptive and least confusing to group all those diseases that share some, but not all, of the molecular properties described for prions found in TSEs.

Because of the different proteins involved in, and clinical signs of, the above disorders, it was initially assumed that a specific pathogenic mechanism was responsible for each of the various diseases. However, similarities emerged during the early 1980s when meticulous molecular studies, initially describing the biophysical traits of the amyloid deposits [10,11], were rapidly followed by the identification of a common process responsible for the misfolding and amyloid aggregation of disease-specific proteins. A key step forward was provided by Stanley Prusiner over two decades ago who, within the frame of the protein-only-hypothesis [12], proved experimentally that the TSE etiologic agent was the self-templated misfolding of PrP^C into an infectious and neurotoxic isoform, PrP^d [13]. More recent research has proposed (and generally proven) that the seeding ability, the aggregate-prone feature and the cell-to-cell transmission characteristic of prions, may also pertain to other proteins eventually generating amyloid plaques [14], e.g., Aβ and tau, α-synuclein, SOD-1 and TDP-43 [15–18]. It is important to mention, however, the frequently detected uncoupling between the cognitive decline in the mentioned disorders and the amyloid load, and the finding that soluble oligomers are the likely neurotoxic species that form early in the protein misfolding cascade [19]. Sadly, the precise mechanism leading to synaptic dysfunctions and neuronal death, and the formulation of potentially common therapeutic approaches, are not yet available. Attention will thus be devoted to whether or not prions and prion-like proteins have common pathological mechanisms and potential inter-individual transmissibility.

Finally, because the intriguing strain-like variability has long been suspected and thoroughly studied in the prion field, the possibility that this concept can also apply to each neurodegeneration-causing misfolded protein will be discussed in detail. Importantly, this issue links to the classic axiom “one protein - one structure” (paraphrasing Anfinsen concept) [20] that several reports apparently now render obsolete [21–25]. In the prion field, for example, by studying the biochemical and structural traits of PrP^d isolated from different TSEs it transpired that different conformations were generated from an identical amino acid sequence with identical post-translational modifications. Following the statement by Balch et al.: “The misfolding and aggregation of proteins is often an accident waiting to happen. Consequently, organisms have developed sophisticated chaperone and quality-control systems to limit abnormal protein interactions and the accumulation of toxic aggregates” [26], and the recent description of strain-like variants of several misfolded proteins, it seems that the above statement can be further expanded such that, if a protein is able to misfold naturally, almost unavoidably it may be able to acquire a diversity of misfolded forms.

A detailed description of traits putatively shared by disease-related misfolded proteins will now be given and discussed.

1.1. Self-templating, propagation and spreading

1.1.1. Transmissible Spongiform Encephalopathies (TSEs)

TSEs or prionopathies are a group of neurodegenerative disorders affecting several mammalian species including humans, characterized by spongiform changes in the brain, synaptic dysfunction, neuronal loss and variable amyloid deposits. As mentioned, these features are related to the conformational misfolding of PrP^C into a β-sheet rich, transmissible and aggregation-prone isoform named PrP^d. The initial misfolding event can be spontaneous, or caused by mutations in the gene coding for PrP^C (as in familial forms of the disease), or because PrP^d is acquired from prion-affected materials of the same or different species [5].

Please cite this article in press as: H. Eraña, et al., Prion-like disorders and Transmissible Spongiform Encephalopathies: An overview of the mechanistic features that are shared by the various disease-related misfolded proteins, Biochemical and Biophysical Research Communications (2016), http://dx.doi.org/10.1016/j.bbrc.2016.08.166