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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 (PrPd), is a self-propagating β-sheet rich aberrant conformation of the cellular prion protein (PrPC) with neurotoxic and aggregation-prone properties, capable of inducing misfolding of PrPC molecules. PrPd 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.

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To the Guest Editor,

Dear Dr Sorgato,

Please find enclosed the **review** entitled " **Strain phenomenon, an intrinsic feature of prion-like disorders**" which we are submitting (after reviewing) for your consideration to be published in BBRC (special issue Stem Cells), **Si:Neurodegeneration**.

Yours sincerely,

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***Response to Reviewers**

Dear Editor,

Thank you very much for considering our manuscript and for the thorough revision which undoubtedly will improve its quality.

We have introduced all the suggested changes.

I am sure that this new version of the manuscript has been strongly improved.

Sincerely,

Joaquín Castilla

Highlights

- Protein misfolding-related disorders share molecular mechanisms with prion diseases
- Common mechanisms include self-templated propagation and spreading at least
- There are growing evidences supporting other shared features as strain variability
- Transmissibility, often confused with infectivity, needs to be further assessed
- Grouping these disorders under a common term requires assessing all the mechanisms

Prion-like disorders. An overview on mechanistic features shared with Transmissible Spongiform Encephalopathy- causing prions

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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.

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 (BSE) 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 [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 characterised, 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 Afinsen 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 and colleagues (2008): "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.

Self-templating, propagation and spreading

Transmissible Spongiform Encephalopathies (TSEs)

TSEs or prionopathies are a group of neurodegenerative disorders affecting several mammalian species including humans, characterised 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, infectious, 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]. Initially considered impossible, it is now widely accepted that PrP^d serves as template for the conversion of PrP^C [13] and recent research suggests that this mechanism may occur in other protein-related disorders [27-30]. Transmissibility of the TSE-causing infectious agent became evident as early as scrapie was described, given the spreading of the disease among animals of a flock. Due to the limited knowledge on molecular biology, until the 1960s most of the theories on TSE etiology were directed to the "slow virus" hypothesis [31]. It was the observation that physico-chemical methods able to neutralize virus were useless to inactivate the TSE-causing agent the first clue about its particular nature [21, 32-35]. In light of this evidence, Griffith proposed that the scrapie agent was proteinaceous and also offered possible mechanisms to explain how a protein could be infectious and how could be controlled genetically or either occur spontaneously [12]. Based on this theory, Prusiner coined the term prion (*proteinaceous infectious particle*) and undoubtedly demonstrated its proteinaceous nature by inactivating the agent by methods that destroy proteins [21, 36]. The search of the gene encoding

this infectious protein revealed soon that it was a host cellular gene expressed in both infected and uninfected brain tissue [37, 38]. The immunity of transgenic mice devoid of this gene to prion infection showed that the pathogenic form of the protein was propagated at the expense of the cellular isoform [39]. Using biophysical techniques, it became clear that PrP^{C} and pathogenic PrP^{d} differed in their structural arrangement [40, 41]. Finally, although detailed molecular mechanism is still lacking, the structural differences shown by different prion strains and the conservation of the particular structural features upon transmission to new hosts, established the self-templated misfolding induction as the propagation mechanism for the TSE-causing agent [42-44].

Further confirmation of the protein-only hypothesis was provided by the development of *in vitro* methods which allowed the generation of infectious prions from recombinant prion protein produced in bacteria [45]. The spreading of prions – that is to say, the distribution over an area of space – either from cell-to-cell, from one tissue to another or from an affected individual to another, is determined by their self-templated propagation mechanism coupled to the ability of overcoming the protein-quality-control mechanisms in the cell [46, 47]. The cell-to-cell spread of prions seems to be aided by their close proximity [48, 49] and PrP^{C} attachment to the external cell membrane through a glycolipid anchor [50, 51]. This can occur in association with exosomes or other vesicles [52-54] or through tunneling nanotubes [55]. In order to cause disease, TSE agents must invade the central nervous system (CNS). Thus, spreading between tissues is required after peripheral infections such as oral exposure or blood transfusion. In the first case, prions are taken up by Peyer's patches and transferred to the surface of cells from the lymphoreticular system and then to enteric nerves and to the CNS [56, 57]. However, alternative routes can be used in the case of blood transfusions [58, 59] or intra-tongue inoculations [60]. Finally, host-to-host spread of prions, which defines their transmissibility, is also well documented and is aided by the high physico-chemical resistance of the agent [61]. Actually, prion shedding via skin, feces, urine, milk, nasal secretions, saliva, placenta and carcasses has been reported [62-64]. Indeed, any protein could show prion-like propagation if it were able to acquire a distinctive folding capable of converting adjacent proteins with identical, or similar, amino acid sequences. As long as this conformer can migrate or be transported cell-to-cell and tissue-to-tissue, its spreading can be considered prion-like. In essence, prions or prion-like proteins would be those proteins able to transfer biological information protein-to-protein through a self-templating conformational change.

Alzheimer's disease (AD)

Characterized by the presence of extracellular amyloids, intracellular and extracellular neurofibrillary tangles (NFTs) and neuronal loss, AD is another example of neurodegeneration involving self-templating amyloidogenic proteins. Amyloids are mainly composed of Aβ peptides of

different length (Aβ40 and Aβ42) originating from a heterogeneous processing of the Amyloid Precursor Protein (APP) by β and γ-secretases. Aβ peptides form oligomeric complexes that eventually assemble into amyloid plaques [65]. Also NFTs are tightly packed protein filaments composed of the hyper-phosphorylated tau protein, which physiologically acts to stabilize microtubules [1]. Due to mutations in the APP processing found in the familial forms of AD, the possible role of tau as the primary cause of AD has received much less attention [65]. This is despite alterations in tau leading to paired helical filaments prior to NFTs formation in AD, which are also found in the large group of neurodegenerative disorders identified as non-AD tauopathies, including FTD [1]. The self-templating propagation or seeding ability of both Aβ and tau has been well documented in several *in vitro* systems [66-73], and their cell-to-cell propagation mechanism has been shown also in cell culture models [17, 72, 74-78]. However, there is now little doubt with respect to self-templating propagation and spreading of Aβ and tau as they have been experimentally reproduced using *in vivo* models [79]. Experiments performed in the early 1990s by Baker and collaborators, in analogy to experiments performed to validate the prion transmissibility [80-82], consisted in inoculating marmosets intracerebrally with brain extracts from human patients with β-amyloid plaques and angiopathy. Although they lacked AD-typical NFTs, the presence of β-amyloidosis in these inoculated animals suggested that β amyloid-containing brain extracts were the seed causing this [83]. Although macaques similarly inoculated behaved likewise [84], these animal models were abandoned with the advent of transgenic mice over-expressing one or more of the human familial AD mutations, as they re-created the human disease with shorter incubation periods. Furthermore, as the majority of models reproduced the spreading of protein misfolding but differed in propagation rates, affected brain areas and the number and type of implicated protein, they can be regarded as proper tools to study transmissibility of exogenous Aβ [85-94] or tau [15, 95-99] aggregates and to verify the prion-like behavior of, if not the cross-seeding between, the two proteins [100-103]. Importantly, a few studies on animal models proved that the seeding activity could be blocked by treating exogenous aggregates either chemically [104] or with anti-Aβ antibodies [105], as was previously observed for prions [106].

A special mention is deserved to the recent evidence of a likely exogenously-induced Aβ seeding in humans. Several patients following treatment with prion-contaminated growth hormone not only developed iatrogenic CJD but also amyloid-β pathology and cerebral amyloid angiopathy, in contrast to age-matched, prion disease-affected individuals. These astonishing data suggest a possible iatrogenic form of AD and cerebral angiopathy, acquired through Aβ–containing growth hormone preparations [107, 108].

Parkinson's disease (PD)

With respect to PD, the seeding ability of α-syn has been proven recently in *in vitro* models [109, 110], including Protein Misfolding Cyclic Amplification [111] originally developed in the prion field, while the cell-to-cell spread was observed in cell culture [78, 112-117]. A particularly remarkable study of the latter type showed that morphologically different intracellular α-syn aggregates correlated with the fibril morphology used as a seed. This supports the idea that PD pathology spreads by conformational dependent self-templating mechanisms [118]. Systemic or intracerebral inoculation in transgenic, and/or wild type, mice of synthetic or brain derived aggregated α-syn, further supports the prion-like seeding and spreading ability of the PD-causing protein [119-123]. Possible direct evidence of this phenomenon can be found in PD-affected individuals who were recipients of neuronal transplants, given that their neural grafts showed Lewy body-like structures composed of post-translationally modified α-syn. Thus, aggregation and deposition in transplanted dopaminergic neurons could have been caused by the misfolded α-syn in the host brain [124-128].

Amyotrophic Lateral Sclerosis (ALS)

One of the most recent members joining the "prion-like disorders" group is ALS**.** ALS is a fatal, rapidly progressing neurodegenerative disease affecting upper and lower motor neurons and characterised by progressive paresis that eventually ends in respiratory failure [129]. As pathological hallmarks, ALS neurons and glial cells show abnormal protein inclusions often labeled by anti-ubiquitin antibodies but containing diverse components. In familial ALS (FALS), which represent about 5-10% of all ALS cases, the major protein in the inclusion bodies is Cu-Zn Superoxide Dismutase 1 (SOD-1). Indeed, approximately 10-20% of FALS are caused by mutations in the SOD-1 gene that render SOD-1 prone to adopting detergent-insoluble conformations and to forming aggregates [4]. In the majority of ALS cases, referred to as sporadic ALS, protein inclusions are mainly formed by the TDP-43 protein. However, TDP-43 is also found in some forms of SOD-1 negative FALS and rare FTD cases [4, 130]. Mutations in other proteins have also been linked to FALS, e.g. Fused in Sarcoma/Translocated in Liposarcoma (FUS/TLS), C9ORF72, Profilin 1 (PFN1) and others [130, 131]. Despite the diversity of ALS-related proteins that account for the phenotypical heterogeneity of the disease, pathological and clinical similarities imply the existence of a common pathogenesis which remains elusive. Although the number of different proteins implicated poses an obstacle to distinguishing the causes and consequences of protein aggregates, the pattern of spread of the paralysis along neuroanatomically connected regions, and recent research on SOD-1, TDP-43 and FUS/TLS misfolding and self-templating ability, suggest a common prion-like mechanism [4, 132].

As the first identified disease-related protein in ALS, SOD-1 has been the most thoroughly studied for its prion-like features. Misfolding, aggregation and template-seeding abilities have been

proven *in vitro* using fibrillized recombinant SOD-1 [16, 133, 134] and observed *in vivo* in the spinal cords of animal models of the disease [134]. SOD-1 cell-to-cell spreading capacity has been observed in cell culture models [135-137] and also in transgenic animals designed to code for FALS-linked mutant SOD-1 or over expression of the wild-type form. These animals showed that protein aggregation and formation of inclusions not only depended upon the presence of mutant SOD-1 but also occurred if native SOD-1 was overexpressed [138]. This is analogous to what observed in transgenic models over-expressing wild type PrP^{C} [139].

It has been reported that misfolded SOD-1 spreads from grafts resulting in pathology [140] and that disease spread can be attenuated with vaccination against SOD-1 [141]. A study that thoroughly addressed the issue of exogenous SOD-1 seeding *in vivo* was performed by injecting spinal cord homogenates from a paralyzed mutant SOD-1 transgenic mice into the sciatic nerve of susceptible G85R:YFP mice. These animals subsequently developed widespread inclusion pathology throughout the spinal cord and in the brain [132].

As to the other proteins implicated in ALS, evidence for their prion-like behavior is scarce, possibly because of their more recent identification [142]. However, mutant TDP-43 displays enhanced aggregation and seeding ability *in vitro* [143-145] and in diverse cellular models expressing the mutant protein [143-145]. This became clear in spite of the difficulty in evaluating differences between wild type and mutant TDP-43-expressing cells, owing to the dose dependent toxicity of mutant TDP-43. Interestingly, a recent study showed cell-to-cell spreading of misfolded TDP-43 in a cell culture model. Thus, self-templating and spreading ability of TDP-43 aggregates, derived from cell culture or ALS affected brain was definitively demonstrated in cell culture [146]. Recently developed *in vivo* models for TDP-43-driven pathology, generated in invertebrates, zebrafish and rodents [147, 148], have not yet been used to investigate exogenous seeding but they may soon provide new insights on the role of this protein in ALS as well as on its prion-like behavior.

FUS/TLS and its prion-like features have received little attention, although the aggregation capacity has been studied in a yeast model, where no enhanced aggregation proneness of disease-linked mutants was reported [149]. In the few animal models generated for disease-linked FUS/TLS mutants (*Drosophila* [150-153], zebrafish embryo [154] and rodents [155-157]) neurodegeneration was observed in all of them. Some resulted in characteristic ALS changes and animals expressing ALS-associated FUS/TLS mutants showed FUS/TLS inclusions [153, 154, 156, 157].

Interesting close relationships are now emerging between FUS/TLS and TDP-43. Aggregates present in ALS are able to recruit native FUS/TLS and TDP-43, possibly via seeding through a yeast prion-like Q/N-rich segment that is present in both proteins [4, 158]. Co-expression of both proteins

in *Drosophila* flies results in enhanced neurotoxicity [151] and the phenotype can be rescued by impeding expression of one of the two proteins [150]. Although the synergistic effects of, or interactions between, the different proteins involved in ALS are not yet well understood, a recent report on SOD-1 expressing cells points towards a prion-like cross-seeding mechanism, whereby FUS/TLS and TDP-43 aggregates can induce misfolding of wild type SOD-1. Indeed, intercellular spread of misfolded SOD-1 is not accompanied by TDP-43 or FUS spread, and can be inhibited by depleting SOD-1 by siRNA or antibodies. This suggests that misfolded TDP-43 and FUS may exert motor neuron pathology through the initiation of SOD-1 misfolding that clearly spreads in a prion-like fashion [137]. A bigenic mouse model, generated for SOD-1 and TDP-43 [159], could shed some light on the complex interactions among all these ALS-related proteins and could also be exploited in cross-seeding experiments. However, the ALS scenario is becoming more complex in light of other proteins that could play a role in the disease by interacting with the classical ones. A case in point is the work by Tanaka and collaborators, who found PFN1 gene mutations in ALS affected individuals and who, through co-expression experiments, showed that PFN1 mutants can function as a seed to induce TDP-43 conversion and prion-like aggregate accumulation [160].

Systemic amyloidoses

There are up to 28 amyloidogenic circulating proteins that can undergo a conformational change giving rise to β-sheet rich, aggregation-prone isoforms that can accumulate as amyloid inclusions [6]. Therefore, reactive amyloid A (AA) amyloidosis will be used as seminal example of systemic amyloidoses. This systemic protein misfolding-related disease appears as a consequence of prolonged or chronic inflammation that rapidly increases the normally low concentration of circulating serum AA protein (SAA). Unknown initiation mechanisms alter its conformation to an amyloidogenic form causing the appearance of life threatening amyloid deposits in most tissues of the body, which are primarily composed of an N-terminal cleavage product of SAA [161]. For many decades now, AA amyloidosis has been studied in laboratory animals, mainly mice, where efficient induction is achieved through a prolonged inflammatory reaction as a result of injection of silver nitrate [161]. The ability of tissue extracts containing AA amyloidosis plaques to accelerate the inflammatory response in mouse models was well known, even before any *in vitro* model had been developed. At that time, the unidentified seeding agent was called Amyloid Enhancing Factor (AEF) [162]. Much later, AEF was definitively shown to be AA, by acceleration of AA amyloidosis through the injection of AA amyloid-composed synthetic fibrils [161]. *In vivo* seeding with AA amyloidosis affected tissues has been further confirmed in mice [163, 164]. Seeding of cerebral AA amyloidosis was shown to be dependent on SAA concentration in mouse models over-expressing SAA in brain or

expressing it conditionally [165]. This phenomenon has also been observed in other animal models such as mink [166], rabbits [167], ducks [168] or chickens [6], in which systemic amyloidoses can be also induced through an inflammatory stimulus.

In concluding this section, the prion-like self-templated propagation and/or seeding ability has been clearly demonstrated for most proteins involved in the above described disorders. Whether this characteristic makes them suitable to be classified as prions depends on the full definition of prions, which will be discussed later. However, in light of the same propagation mechanism, they could definitively be called propagons or more simply prion-like propagating proteins.

Strains and interspecies propagation

Transmissible Spongiform Encephalopathies (TSEs)

One of the most intriguing characteristic of TSEs is that inoculation of different prion isolates containing an identical PrP^C/PrP^d amino acid sequence leads to significantly variable clinical and histopathological manifestations of the disease [169]. Such different properties are defined by distinct self-propagating conformations that the same PrP sequence can acquire, i.e., strains of the same infectious agent that, unlike viral or bacterial strains, encode information through three dimensional structures [170]. The strain-specific properties of prions include different tropism for certain brain regions [171, 172], formation of morphologically distinct aggregates with different physicochemical properties [43, 173] and different self-templating and cross-seeding capacities [174]. The latter is particularly important in the field of TSE, given that some prion strains can propagate at the expense of PrP^C with slightly different amino acid sequence, which results in interspecies transmission of the disease. Although the ability of heterologous seeding lies ultimately on the tertiary or quaternary [175] structure of each prion strain, the more distant is the primary structure between the misfolded protein and the host native PrP^C, the more difficult the propagation will be. This phenomenon, well-known in the prion field as the interspecies transmission barrier, which manifests with a prolonged incubation period of the disease and as an incomplete attack rate among the infected animals [176]. The emergence of different prion strains is probably due to the conformational variability derived from the PrP-misfolding event, which gives rise to PrP^d isoforms that maintain their structure through the self-templated propagation mechanism. Thus, taking into account the similar misfolding and propagation mechanisms, certain strain-like variability and interspecies transmissibility would be also expected in other prion-like disorders. Therefore, the

description of such a characteristic, intrinsically associated to TSE-causing prions but applied to the other proteins, would speak in favor of their inclusion in the prion-like protein club.

Alzheimer's Disease (AD)

The ability of Aβ and tau to adopt slightly different structures with different biochemical properties, which can be also propagated in a stable manner, has already been proven in several model systems. Most of the evidence regarding Aβ strains comes from Mathias Jucker's group. Using two different AD transgenic mouse models inoculated with brain extracts from each other, they showed that both animal models developed clearly distinguishable, brain extract-specific aggregates [86, 177]. These results have been recently reinforced in cell cultures experiments demonstrating that the conformation-specific propagation of Aβ isoforms manifests with distinct toxicities [70] and aggregate clearance capacities [178]. The latest demonstration for the existence of distinct Aβ strains has been recently provided by the prion strain-expert laboratory of Stanley Prusiner. Using a bigenic mouse model, they showed that injection of different synthetic Aβ fibrils, composed of either Aβ40 or Aβ42 peptides, caused markedly different β-amyloids; while Aβ40 induced plaques containing both Aβ40 and Aβ42 within long straight fibrils, Aβ42 induced more numerous depositions containing mainly Aβ42, and composed of much shorter fibrils. They also showed that this phenomenon is fully conformation-dependent and independent of the Aβ species used [179]. Taking a step further, the existence of different strains in AD patients was proved because injection in the above bigenic mouse line of brain homogenates from patients carrying the Swedish or Arctic APP mutation, or affected by sporadic AD, resulted in a pathology that was clearly distinguishable according to the brain homogenate used. Importantly, the different Aβ isoforms present in the inclusion and the plaque morphology were conserved after a second passage in the same mouse line [180].

Although scarce, there are studies that support the possible existence of tau strains, and that the wide phenotypical variety of tauopathies could be based on tau conformational differences. Indeed, different spread patterns have been observed in wild type- or mutant tau-expressing models [181]. Also, it was observed that either *in vitro* produced fibrils [182], or brain extracts from patients with different tauopathies, induced differential spread and deposition patterns in the human P301S tau expressing mouse line, and that these features were conserved upon serial passage [183]. Finally, two very recent studies demonstrated that human tauopathies can be classified according to the distinct biochemical properties of the tau aggregates [184], and that distinct aggregates show different seeding potencies in cell culture [185].

In light of these results, it may be possible to envision the capacity of some strains to seed proteins from other species, a concept that is reminiscent of the interspecies transmission of TSEs. In this regard, the most significant findings were accumulated in tauopathy models expressing mouse tau and/or human wild type and mutant tau forms, where murine tau interfered with the human isoform by reducing aggregation and the extent of the induced disease [186, 187]. Along this line, the existence of interspecies barrier and transmissibility has already been proved for human and mouse tau *in vivo*. On the one hand, because several human brain extracts with different tau aggregate-related diseases were able to induce mouse tau aggregates in wild type mice [97]. And on the other hand, because human and mouse tau have been shown to co-aggregate in transgenic mouse lines conditionally expressing disease-associated human tau as well as the endogenous mouse tau [188]. On the contrary, although endogenous mouse and mutant human Aβ were found to co-localize in a human-APP/PS1 double transgenic mouse model [189], more data are needed to firmly establish some kind of interspecies transmission barrier, as co-localization does not necessarily imply co-aggregation.

Parkinson's Disease (PD)

Considering α-syn aggregates, either associated with PD and with phenotypically distinct synucleinopathies, there is little evidence for the existence of conformational variants acting as strains. However, in *in vitro* and cell culture models it was reported that different synthetic α-syn conformers are capable to inducing distinct effects and to self-propagate in a stable manner [190]. More importantly, differences were detected in cell cultures between two *in vitro*-produced misfolded α-syn variants in terms of structure, cell uptake and binding, toxicity and aggregation patterns [191]. Again, it was Prusiner's lab who reported a more convincing study on α-syn strain properties. Using 14 brains from patients affected by Multiple System Atrophy (MSA, a α-synucleinopathy slightly different from PD) to inoculate cell cultures and a transgenic mouse model expressing human α-syn, they observed that, contrary to brain extracts from PD patients, MSA extracts were able to propagate in the cell culture model and to induce disease in transgenic animals. This result suggests that a unique strain of misfolded α-syn is that causing MSA [192], and is supported by a similar study showing that morphologically different aggregates - characterising three α-synucleinopathies, i.e., PD, dementia with Lewy bodies and MSA - propagated in a strain-dependent manner and induced distinct pathologies after injection into rats [193]. Finally, it is worth mentioning an unconventional *in vivo* study, in which inoculation in the P301S tau expressing mouse model of two *in vitro*-generated α-syn fibril types resulted in a different behaviour of the two conformers with respect to: i) cross-seeding ability of tau, ii) induction of α-synuclein pathology, iii)

toxicity, and iv) electrophoretic pattern of α-syn after proteinase K digestion. Of importance, the latter feature was also found in human samples from patients with different synucleinopathies [194].

As for tau, some kind of interspecies transmission barrier could also pertain to α-syn, according to a study using mice expressing human α-syn that, after inoculation with PD brain extracts, showed much faster and stronger induction of pathology than wild type mice. Likewise, inoculation of recombinant human or mouse α-syn fibrils in wild type mice resulted in a slightly higher efficiency of the mouse seeds compared to the human ones, again resembling the prion interspecies transmission barrier [121].

Amyotrophic Lateral Sclerosis (ALS)

Thus far, scarce evidence is available for the existence of conformational variants behaving as strains in ALS-related proteins such as SOD-1 and TDP-43. Yet, Bidhendi and collaborators have shown that two different SOD-1 aggregates can arise in a mouse model expressing a human disease-linked SOD-1 mutant, and that inoculation in the same mouse line of brain extracts containing each of the two aggregates caused pathologies with different progression rates, distribution, end-stage aggregate levels and histopathology [195]. Although at present this is the only evidence of strains deriving from the same (albeit mutated) amino acid sequence, recently Ayers and collaborators have reported a strain-like behavior in two transgenic mice models expressing SOD-1 with two distinct pathogenic mutations, as the injection of spinal cord extracts from the above models in a highly vulnerable third animal expressing another disease-linked SOD-1 mutant, gave rise to strikingly different phenotypes [132]. Similarly, co-aggregation of human wild type and mutant SOD-1, but not of mouse SOD-1, has been reported in some animal models [196]. Further investigations in cell models have identified in a single amino acid the responsibility for the mouse-human SOD-1 barrier [136].

TDP-43 aggregates from ALS and FTD patients have been used to seed aggregation in human TDP-43 expressing cells. The resultant insoluble inclusions showed the same immunoblot pattern as those observed in the original seeds, suggesting that ALS and FTD could be caused by different TDP-43 conformers [18]. Similar conclusions could be drawn from experiments using cell cultures that, seeded with different peptides arising from distinct TDP-43 C-terminal deletions, showed biochemically distinguishable TDP-43 aggregates [197].

Systemic amyloidoses

Contrary to the above-examined disorders, no experimental evidence has been reported so far for the existence of strain features pertaining to AA amyloidosis. However, although most common AA-amyloidoses are formed by just one gene product, two histopathologically and/or biochemically distinguishable kidney phenotypes have been observed in patients. In general, kidney amyloidosis severely affects glomeruli but in few cases vascular amyloidosis was observed, with a characteristic pattern present also in the plaques deposited in other organs. The reason leading to the two phenotypes is unknown but conformational variants of the same SAA protein have been proposed [162]. A study performed in goats affected by systemic AA amyloidosis is also suggestive of different SAA deposition patterns, whereby uterine depositions seemed composed of a different SAA compared to the most common deposits in liver or other sites [198].

Heterologous transmission of AA amyloid fibrils has been shown in several species, e.g., from cheetah or bovine to rodent models [167, 199-201]. In particular, the slightly milder pathology that was described in mice by Cui and collaborators after heterologous induction experiments is reminiscent of what was observed in TSE interspecies transmission [199].

In concluding, the reported existence of different conformers, and strain behavior, of all the here-reviewed proteins, adds another support to the prion-like character of those proteins whose misfolding profoundly affects viability of different organs.

Infectivity

Transmissible Spongiform Encephalopathies (TSEs)

Before discussing whether each of the above-mentioned misfolded proteins are infectious in the same way TSE-causing prions are, “infectivity” needs to be clearly defined. Given that in many cases, infectivity is wrongly associated with disease or transmissibility. In a broader sense, infectivity means the invasion and multiplication of a self-perpetuating agent in a host body tissue, whether the agent is able to cause disease or not. The ability of an infectious agent to cause disease is defined as pathogenicity and it depends on the host as much as on the infectious agent. Thus, it is necessary to keep in mind that not all the agents able to invade and multiply in other organism (infectious agent) cause disease (pathogen) [202, 203], as shown by asymptomatic carriers of prions [204]. The pathogenicity of an infectious agent is not entirely dependent on the agent itself but also on the suitability of the new host. This is clearly illustrated by the poor pathogenicity of vCJD on hosts carrying V129 polymorphism [205]. Similarly, inter-individual transmissibility is often wrongly considered as an intrinsic characteristic of infectious agents, however, it is defined as the efficiency with which an infectious agent can be transmitted to a naïve host and it depends also in the

suitability of the host and the existence of a route by which the agent reaches it [202, 203]. For example, several GSS isolates that are clearly infectious - because they can multiply in host tissues - have been long considered poorly infectious. However, they should have been considered poorly transmissible just to certain hosts, as they have been shown to be highly transmissible and pathogenic as long as the right model is used [206, 207].

Therefore, we consider TSE-causing prions infectious because they are able to invade and self-perpetuate in body tissues, regardless of their ability to cause disease or be transmitted between individuals. Thus, from our point of view, the self-perpetuating characteristic of the proteins implicated in AD, PD, ALS and AA amyloidosis define them as infectious. Actually, irrefutable proofs of infectivity – understood as ability to self-perpetuate in body tissues - and transmissibility of Aβ peptides were recently reported. Autopsy of CJD-contaminated growth hormone recipients, that also contained Aβ peptides from the donors, showed unusually high presence of Aβ aggregates. However, its pathogenicity could not be demonstrated given the early death of the patients caused by iCJD [107, 108] or other unrelated pathologies (Ironside J.W., Oral communication, Prion 2016 Congress, Tokyo).

Nevertheless, as "infectivity" is commonly used confused with the concepts of pathogenicity or transmissibility, autocatalytic propagation and spreading features are not sufficient to consider certain agent "infectious". For that, proofs of inter-individual transmissibility are demanded, and in the case of neurodegenerative diseases the ability to invade the CNS when exogenously acquired, i.e., from affected hosts or from the environment [14]. Moreover, for TSE-causing prions, transmissibility needs to be shown in animal models in which the pathological processes would not occur spontaneously, thus, *de novo* induction of the disease should be clearly established.

Therefore, despite the misfolded proteins implicated in AD, PD, ALS and AA amyloidosis have an established prion-like self-perpetuating characteristic, they are not generally considered "infectious" - in the same way as TSEs - unless their pathogenicity, inter-individual transmissibility and an acquisition route for exogenous agents are demonstrated. Thus, the updated state of the art on these issues is now given.

Alzheimer's Disease (AD)

For AD, possible inter-individual transmission by routes more "natural" than intracerebral inoculation has been tested, yet not definitively proven.

Initial trials of peripheral (oral, intravenous, intraocular or intranasal) inoculation of Aβ-rich extracts in APP transgenic mouse models showed no induction of cerebral amyloidosis [88], although their intraperitoneal inoculation did cause blood-vessel associated Aβ deposits [208]. More recently, it has been reported that intraperitoneally injected Aβ seeds propagated to the brain of three transgenic mouse lines expressing different APP levels, that amyloidosis could be impaired by antibodies to Aβ, and that the severity of the pathology depended also on brain APP amounts [105]. Using similar mouse models, cerebral Aβ amyloidosis could also be induced by the intraperitoneal inoculation of synthetic Aβ fibrils [209]. Likewise, the intraperitoneal injection of tau aggregates in a mouse model expressing a disease-linked tau mutant successfully induced tau pathology - albeit in a less severe form than that caused by an intracerebral route [210].

It is important to note, however, that all the above animal models developed Aβ amyloidosis or tauopathy upon aging, opening the possibility that exogenously acquired seeds were accelerating the endogenous pathology rather than inducing it *de novo*. The absence of good epidemiological data [211], and the definitive proof of peripherally induced pathology in non-susceptible animal models prevent, therefore, to consider AD "infectious" as prions are.

As was the case with initial studies in the prion field, more appropriate models are needed to prove Aβ and tau infectious characters, especially because availability of recent animal models for prion disease has allowed to prove the infectious properties of certain prion strains that for decades were considered poorly, if not at all, transmissible [206, 207]. This actual AD scenario could, however, change soon in light of the earlier mentioned findings that growth hormone preparations not only induced iatrogenic CJD but also cerebral amyloid β pathology and angiopathy [107, 108].

Parkinson's disease (PD)

Evidence for the peripheral routes of disease acquisition are uncommon in PD, although it is well known the inter-individual transmissibility by contaminated grafts [124-128], and a possible route of neuroinvasion by exogenous PD brain extracts. The presence of α-syn aggregates in enteric neurons [212], secretions [213], or circulating in body fluids (e.g., plasma) [214] of animal models injected peripherally with PD samples from patients, has pointed to the possible induction of pathology. A PD-like pathology was observed by injection of brain extracts directly into the gastric walls of a transgenic mouse model expressing mutant α-syn, suggesting that the enteric nervous system could be a natural route for neuroinvasion [215]. Furthermore, the neuroinvasion capacity of the aggregates was definitively proved by the finding of cerebral synucleinopathy following intravenous administration of distinct α-syn aggregates in α-syn-expressing rats [193].

Amyotrophic Lateral Sclerosis (ALS)

In the case of ALS, further experimental evidence is required to show possible inter-individual transmissibility from routes other than the direct injection of aggregates into the nervous system, in which prion-like spreading through anatomically-connected neuronal pathways has been shown [216]. Even though the presence of extracellular or exosomal aggregates was found in cell culture models [137, 146, 217], there is still little evidence for ALS peripheral, prion-like transmissibility *in vivo*.

Systemic amyloidoses

Because AA amyloidosis is a systemic condition where no neuroinvasive routes are required, proofs of inter-individual transmissibility are easier and indeed have been widely accumuleted. for example, successful transmission experiments were performed by administering the seeding material either intraperitoneally or intravenously. Importantly, the oral route of transmission was found effective in inflammatory stimulus-induced mice [163], but also in IL-6 over-expressing mice fed by commercially available duck *foie gras* [200].

Although the initial seeding site is unknown, probable tissue-to-tissue propagation pathways take place as suggested after intravenously injected radiolabelled fibrils accumulated in the spleen [161] or circulating monocytes [218]. However, although successful experimental transmission has been reported in several animal models, and also from one species to another [6], non-experimental seeding of AA amyloidosis is more difficult to prove definitively. Nonetheless, some epidemic outbreaks of AA amyloidosis in captive animals [6], together with the potential transmissibility of AA amyloidosis from cheetah feces to mouse models [201], suggests that non-experimental horizontal inter-individual transmission is feasible, similarly to some TSE forms [219].

CONCLUDING REMARKS

From what discussed hitherto, and the evidence for similarities and dissimilarities between prions and the other disease-related misfolded proteins, grouping all of them under the term “prion” seems not fully congruent [220]. In our opinion the term “prion-like diseases/agents”, which is here preferentially used, describes more accurately those misfolded proteins that clearly share similarities with some molecular aspects of the mammalian prion protein, the self-perpetuating aggregation and spreading characteristics, for example, and appears, therefore, the most suited, at least until other commonalities or differences are definitively proven [221]. The newly coined “prionoid” or “propagon” terms have been proposed, since none of these misfolded proteins were shown to be

highly transmissible under natural conditions [9, 222]. However, we believe somehow premature the introduction of these new nouns, given that many common or different molecular features of the above-mentioned proteins still need to be assessed.

Undoubtedly, issues such as infectivity and/or inter-individual transmissibility are the most critical for classifying misfolded protein-related diseases under a common name. The neurotoxic mechanism of the protein aggregates involved in each disorder remains poorly understood, as is the possible inter-individual transmission by natural routes. Both of them represent the crucial mechanistic features that could differentiate prion-causing TSEs from the other diseases. Indeed, most TSEs are clearly transmissible, as evident from epidemics that have affected several mammalian species [223-226], and demonstrated after the peripheral prion invasion of inter-individual iatrogenic disease transmission [227], or after the oral or intraperitoneal prion administration [228, 229]. Conversely, thus far all these proofs are not yet fully available for AD and PD. We believe, therefore, that the meaning of "infectivity" needs to be reassessed to encompass new circumstances, possibly including a process in which a self-propagating agent that exogenously penetrates an organism, or is generated spontaneously, interacts with the host (causing disease/damage or not), as a consequence of its intrinsic capacity to make copies of itself through a diversity of mechanisms. Only after introducing these new aspects, and the mechanisms of neurotoxicity are clearly established, the use of the terms prion or prion-like to collectively group all these disorders will become evident.

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***Conflict of Interest**

- No conflict of interest.