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From nucleation to widespread propagation: A prion-like concept for ALS

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ABSTRACT

Propagation of pathological protein assemblies *via* a prion-like mechanism has been suggested to drive neurodegenerative diseases, such as Parkinson's and Alzheimer's. Recently, amyotrophic lateral sclerosis (ALS)-linked proteins, such as SOD1, TDP-43 and FUS were shown to follow self-perpetuating seeded aggregation, thereby adding ALS to the group of prion-like disorders. The cell-to-cell spread of these pathological protein assemblies and their pathogenic mechanism is poorly understood. However, as ALS is a non-cell autonomous disease and pathology in glial cells was shown to contribute to motor neuron damage, spreading mechanisms are likely to underlie disease progression *via* the interplay between affected neurons and their neighboring glial cells.

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1. Prions and prion-like events in neurodegeneration

Neurodegenerative diseases, such as Alzheimer's or Parkinson's disease, are among today's major public health issues. Despite decades of extensive research on the molecular mechanisms driving neurodegeneration, no consensus has yet emerged, thus making it more challenging to develop effective therapies. A common feature of neurodegenerative diseases is the accumulation of misfolded proteins in affected regions of the central nervous system (CNS). The main protein component of these pathological deposits may be unique for each disorder, *e.g.* α-synuclein in Parkinson's disease (PD) or β-amyloid in Alzheimer's disease (AD). Moreover, some conditions are characterized by accumulation of more than one misfolded protein. For instance, pathological tau and β-amyloid are the primary pathologies in AD, but secondary pathologies, such as TDP-43 (Amador-Ortiz et al., 2007; Uryu et al., 2008) and α-synuclein (Hamilton, 2000; Higashi et al., 2007), also occur in ~30–40% of AD patients. In addition, one type of aggregated protein may be observed in multiple disorders, such as TDP-43, which is found abundantly in the pathogenic inclusions of patients with amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD) (Arai et al., 2006; Neumann et al., 2006), but also many other diseases, including a fraction of AD and PD cases (Banks et al., 2008; Lagier-Tourenne et al., 2010; Walker et al., 2014).

In the recent years, increasing evidence supports a common mechanism driving neurodegeneration in many clinically diverse conditions. This pathogenic mechanism involves formation of aberrant protein aggregates, which is propagated in a self-templating manner (Fig. 1A). Indeed, misfolded protein assemblies have been shown to act as seeds of aggregation that can sequester their native isoforms and convert them into pathological molecules, thereby growing in size. Subsequent fragmentation of the aggregates and repetition of the cycle leads to amplification of the pathological state within one cell, as well as through the nervous system *via* the release of seeds to the extracellular space, uptake by the neighboring cells and repetition of the propagation cycle.

This mechanism, resembles the replication of infectious prions, and is therefore often termed "prion-like" (Goedert et al., 2010; Guo and Lee, 2014; Jucker and Walker, 2013; Polymenidou and Cleveland, 2011, 2012). Prion diseases, also called transmissible spongiform encephalopathies, are neurological disorders, which unlike any other human neurodegenerative disease, can be transmitted between individuals. The infectious agent is the prion, which consists only of misfolded pathogenic protein (Prusiner, 1982). Besides infectious etiology, prion diseases, like other neurodegenerative disorders, can have sporadic or familial origin. In the latter, heritable mutations occur in the *PRNP* gene encoding the cellular prion protein. The disease mechanism is based on the conversion of the normal cellular isoform of the prion protein, PrP^{C}, to a misfolded highly aggregative form, PrP^{Sc}, triggering a widespread misfolding and fibril formation across the nervous system in a

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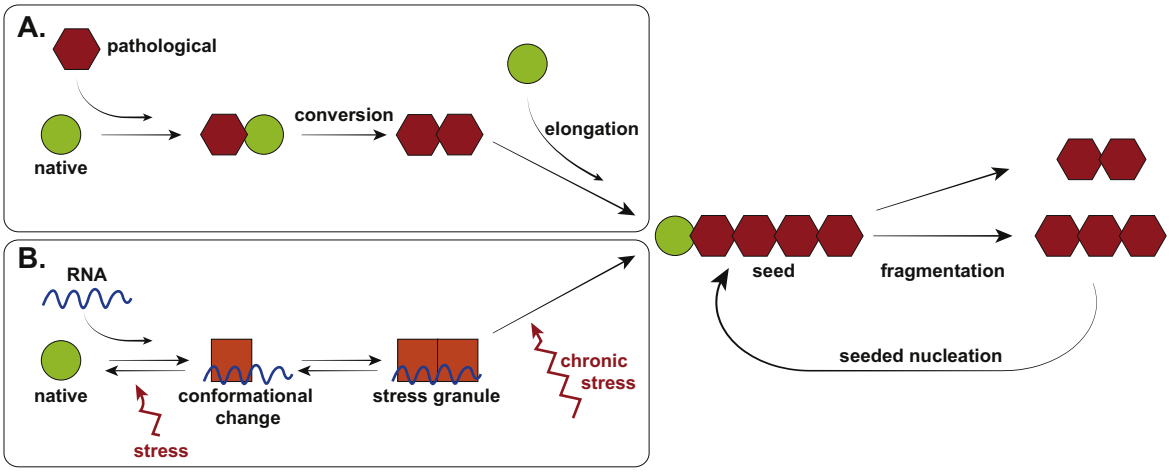

Fig. 1. Prion-like propagation mechanisms. (A) In the classical view of prion-like amplification of pathological protein conformation, the misfolded protein interacts with its native counterpart and converts it into a pathological molecule. This aberrant aggregate elongates by recruitment and conversion of further native protein, which produces a highly ordered seed of aggregation. The latter eventually fragments, resulting in multiple seeds, which induce next cycles of seeded nucleation and amplify the pathological protein aggregation and disease phenotype. (B) For RNA-binding proteins with prion-like domains, such as TDP-43 and FUS, aggregate nucleation may be initiated within the stress granules, which are highly dynamic and strictly regulated protein–RNA complexes forming in cellular stress conditions. The formation of stress granules involves RNA-binding and conformational change and results in the increase of local protein concentration. In disease, potentially as a consequence of yet uncharacterized chronic cellular stress conditions, the highly concentrated RNA-binding proteins in stress granules may transform into pre-inclusions and eventually convert into irreversible protein aggregates.

self-perpetuating manner (Aguzzi, 2009; Aguzzi and Polymenidou, 2004; Aguzzi and Rajendran, 2009). Indeed, mice lacking the prion protein are completely resistant to prion disease (Bueler et al., 1993). The pathology of prion diseases is characterized by protein aggregation, neuronal loss, gliosis and spongiform degeneration (Aguzzi and Polymenidou, 2004). Moreover, the misfolded prion protein was shown to acquire several different structural conformations, referred to as strains, which lead to development of various disease phenotypes with distinct histopathological signatures, incubation periods and severity of disease progression (Aguzzi et al., 2007).

The recognition that pathological aggregates of β-amyloid, tau, α-synuclein and others behave in a prion-like manner has major implications for disease initiation and progression (Goedert et al., 2010; Guo and Lee, 2014; Jucker and Walker, 2013; Polymenidou and Cleveland, 2011, 2012). Indeed, it has been suggested that most neurodegenerative disorders spread in a spatiotemporal fashion through mechanisms involving the seeded aggregation of pathogenic proteins, which trigger neurotoxicity and eventually neuronal cell death (Aguzzi, 2009; Aguzzi and Rajendran, 2009; Goedert et al., 2010; Polymenidou and Cleveland, 2011, 2012). There is substantial evidence supporting this hypothesis, as amyloid-β (Meyer-Luehmann et al., 2006), tau (Clavaguera et al., 2009; Liu et al., 2012; Nonaka et al., 2010), and α-synuclein (Luk et al., 2012; Masuda-Suzukake et al., 2013; Nonaka et al., 2010; Volpicelli-Daley et al., 2011) aggregates were able to induce native protein misfolding and cell-to-cell transmission, both *in vitro* and *in vivo*.

2. Terminology

While recent evidence indicates that the molecular mechanisms underlying the replication of prions is fundamentally the same with the mechanisms propagating pathological aggregates in other neurodegenerative diseases, there is one substantial difference. There is currently no evidence that any other human neurological disorder, besides prion diseases, can be transmitted from one individual to another (Irwin et al., 2013). Therefore a specific terminology is needed to distinguish them from prion diseases. Since the scientific community has not fully settled on this terminology, we define our interpretation of the most commonly used terms below.

The self-perpetuating propagation of misfolding and aggregation, resembling that of prion amplification, is referred to as 'prion-like' mechanism. The term 'seeding' is used to describe the templated aggregation and conversion of a large amount of natively folded protein into pathological conformation, *via* the introduction of minute amounts of preformed aggregates. Although, seeding is mostly referred to *in vitro* assays on purified proteins, it could be extended to mean the same type of molecular events occurring within a cell. 'Nucleation' refers to the initial phase of the seeding process, namely formation of the seed of aggregation. The propagation of aggregates within one organism, *via* cellular connections, exo/endocytosis mechanisms and possibly other, yet unclarified events, is often called 'cell-to-cell spreading'. Lastly, the term 'prionoid' has been coined to differentiate the pathological proteins causative for prion-like diseases from the *bona fide* infectious prion (Aguzzi, 2009).

Within the recent years exciting reports emerged, suggesting that ALS-linked pathological proteins are indeed prionoids, as they have the potential to seed and propagate their pathological conformation through recruitment of native proteins. Consequently, one major focus of ALS research today is the investigation of the role of seeded aggregation mechanisms in ALS pathogenesis.

3. Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis is an adult-onset neurodegenerative disorder, which is characterized by rapidly progressive weakness and muscular wasting, leading to paralysis and death due to respiratory failure within 1–5 years from disease onset (Ilieva et al., 2009; Polymenidou et al., 2012). ALS is the most common motor neuron disease that affects more than 1 in 100,000 individuals each year. The major risk factor of ALS is age, as the disease most commonly occurs between 40 and 60 years. However, there are other environmental factors that increase the risk of developing ALS, such as lifetime of intensive physical activity (Kiernan et al., 2011; Scarmeas et al., 2002; Veldink et al., 2005), as in the case of professional football players (Chio et al., 2005) or members of the military (Weisskopf et al., 2005).

The majority of ALS cases (90%) presents spontaneous onset without any evidence of inheritance, and is referred to as sporadic ALS (sALS). The remaining 10%, classified as familial ALS

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