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Review Article

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Prion-like Mechanism in Amyotrophic Lateral Sclerosis: are Protein Aggregates the Key?

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ALS is a fatal adult-onset motor neuron disease. Motor neurons in the cortex, brain stem and spinal cord gradually degenerate in ALS patients, and most ALS patients die within 3~5 years of disease onset due to respiratory failure. The major pathological hallmark of ALS is abnormal accumulation of protein inclusions containing TDP-43, FUS or SOD1 protein. Moreover, the focality of clinical onset and regional spreading of neurodegeneration are typical features of ALS. These clinical data indicate that neurodegeneration in ALS is an orderly propagating process, which seems to share the signature of a seeded self-propagation with pathogenic prion proteins. *In vitro* and cell line experimental evidence suggests that SOD1, TDP-43 and FUS form insoluble fibrillar aggregates. Notably, these protein fibrillar aggregates can act as seeds to trigger the aggregation of native counterparts. Collectively, a self-propagation mechanism similar to prion replication and spreading may underlie the pathology of ALS. In this review, we will briefly summarize recent evidence to support the prion-like properties of major ALS-associated proteins and discuss the possible therapeutic strategies for ALS based on a prion-like mechanism.

Key words: ALS (Amyotrophic lateral sclerosis), SOD1, TDP-43, FUS, Plion-like phenomena, Misfolded protein aggregates

INTRODUCTION

The motor neuron diseases (MND) are a class of progressive neurologic diseases characterized by selective degeneration of the motor neurons that govern voluntary muscle movement [1]. Amyotrophic lateral sclerosis (ALS), also called Lou Gehrig's disease, is the most common form of motor neuron disease. It is a fatal adult-onset (the average disease onset age is approximately 50 years) neurodegenerative disease, and major characteristic symptoms of ALS include muscle weakness, spasticity, atrophy, paralysis and premature death [2]. Motor neurons in the cortex, brain stem and spinal cord gradually degenerate in ALS patients, and most ALS patients die within 3~5 years of disease onset due to respiratory failure. However, approximately 10% of patients survive more than ten years [3]. The incidence rate of ALS is 2 out of 100,000 individuals per year, and the average age of onset is approximately 50 years [2]. ALS is sporadic in 95% of patients and seems to occur randomly throughout the population (called Sporadic ALS (SALS)). The remaining 5% of ALS patients have at least one affected first degree relative (familial ALS (FALS)) [4]. There is no cure for ALS, and riluzole, the only FDA-approved drug for ALS treatment, extends survival by only a few months [5]. Thus, the search for novel therapeutic approaches is warranted.

The first identified ALS disease gene was *SOD1* (copper zinc superoxide dismutase 1), which was found in 1993 [6]. Thanks to recent advances in sequencing and genotyping technology, many new genetic mutations have been identified in FALS and SALS patients. These mutations are found in the *HNRNPA1,*

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PFN1, TAF15, ATXN2, C9ORF72, UBQLN2, OPTN, VCP, FUS and *TARDBP* genes [4,7]. Interestingly, the most prominent histopathological hallmark of ALS is the accumulation of misfolded oligomers or protein inclusions containing TDP-43, FUS or SOD1 protein [2]. Moreover, most ALS patients have dense TDP-43 aggregates in affected neurons and glia in the CNS [8].

Despite protein aggregation being a prominent pathological hallmark of ALS, many questions still need to be addressed, especially regarding the pathological role and formation mechanism of these protein aggregates [4]. Recently, it was proposed that cell to cell transmission of misfolded protein aggregates (a prion-like mechanism) may directly contribute to the generation of novel protein aggregates and the propagation of neurodegeneration in ALS and other neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease and Huntington's disease [9-13].

In this review, we highlight the recent findings implicating a prion-like mechanism as a key player in neurodegeneration in ALS patients and discuss the possible therapeutic strategies for ALS based on a prion-like mechanism.

PRION-LIKE PHENOMENA IN ALS

Transmissible spongiform encephalopathies (TSEs), also called prion diseases, are fatal neurodegenerative diseases of mammals. The infectious agent of TSEs is a misfolded protein, referred to as PRP^{sc} [14]. PRP^{sc} aggregates can self-propagate and elongate by binding to monomers of PrP^{c} (normal prion protein) [15]. There are a number of similarities between TSEs and ALS. First of all, ALS patients have an aggregate structure that contains a misfolded self-protein in their affected neurons. Furthermore, recent cultured cell line and animal model studies suggest that the misfolded forms of SOD1 and TDP-43 do self-propagate within neuronal cells and transmit to neighboring cells [9,12,16]. One of the most well-known clinical observations of ALS is focal onset of motor weakness in the spinal and bulbar regions and contagious spreading of the disease [17]. Interestingly, intensive autopsy studies of postmortem ALS patients show that the loss of lower motor neurons is most apparent at the region of onset and decreases in a graded manner with further distance from the anatomic location of disease onset [18]. These clinical data indicate that neurodegeneration in ALS is an orderly propagating process, which seems to share the signature of seeded self-propagation with pathogenic prion proteins.

Despite a number of parallels between prion disease and ALS, the prion-like phenomena observed in ALS are fundamentally different from TSEs. The main characteristic of TSEs is their infectivity. Prion diseases can be transmitted through an animal population via oral uptake, blood transfusion or other sources of direct contact [19]. TDP-43 and SOD1 misfolded protein aggregates found in ALS patients can induce the misfolding of their normally structured counterparts; however, at least under natural circumstances, ALS is not an infectious disease. Therefore, we should differentiate the terms "prion" and "prion-like". The term "prion-like mechanism" will be used to identify the molecular mechanisms that share common features with the self-propagation and spreading characteristics of prion proteins. A summary of the evidence implicating the prion-like mechanism within ALS is shown in Table 1.

PRION-LIKE PROPERTIES OF SOD1

SOD1 is a highly conserved, ubiquitously expressed enzyme that scavenges superoxide radicals [13]. Dominant mutations in the gene encoding SOD1 account for approximately 20% of FALS cases [20]. Native SOD1 forms a very stable homodimer, but almost all ALS-linked SOD1 mutations are susceptible to partial unfolding at physiological pH and temperature [21]. Furthermore, mutant SOD1-containing insoluble inclusions are highly accumulated within affected motor neurons of SOD1-

Table 1. Evidence for prion-like mechanisms in ALS

Aggregated Protein in ALS	Cellular location of Aggregates	Subcellular localization of native protein	Self-propagation			Cell-to-Cell Spread		Transmission to other animals	
			In vitro	In cell culture	In vivo in mice	In cell culture	In mice	Synthetic protein	Brain extract
SOD1	Intracellular [42] Extracellular [43]	Cytoplasmic [23]	Yes [27]	Yes [28]	n.d.	Yes [16]	Possibly [12]	n.d.	n.d.
TDP-43	Intracellular [31]	Nuclear [7]	Yes [11]	Yes [11]	n.d.	Possibly [9]	n.d.	n.d.	n.d.
FUS/TLS	Intracellular [4]	Nuclear [20]	Yes [37]	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.

SOD1: Superoxide dismutase1, TDP-43: TAR DNA-binding protein 43, FUS/TLS: Fused in sarcoma/ translocated in liposarcoma, n.d.: not determined.

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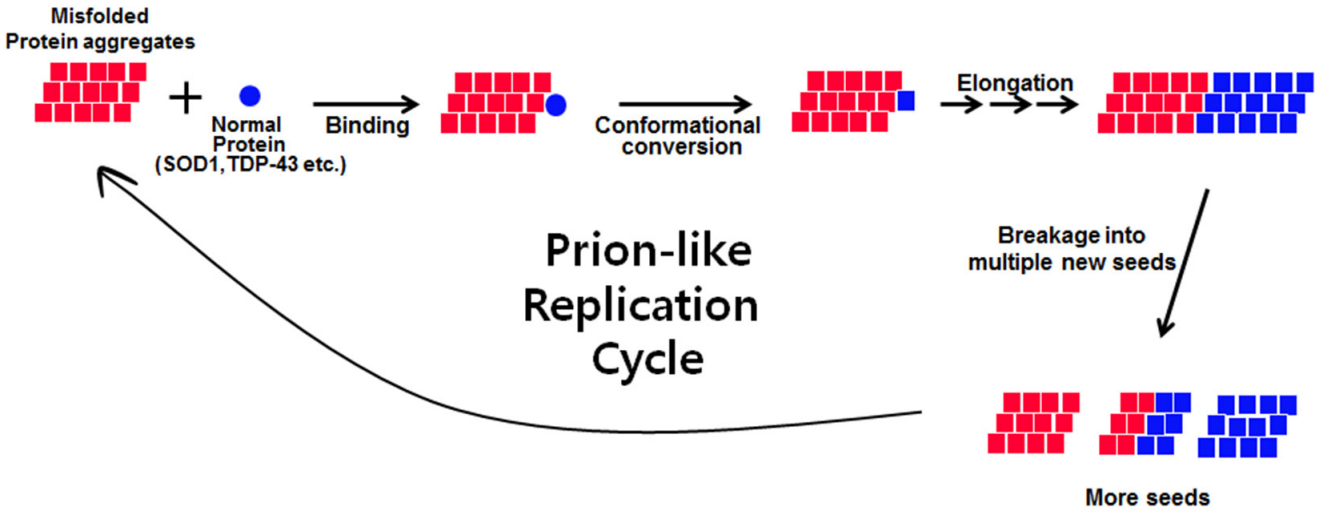

Fig. 1. Proposed model of self-propagation of misfolded protein fibrils in ALS. Misfolded protein aggregates bind to their native counterparts at their end and induce the misfolding of captured protein in a template-directed reaction. This process elongates the misfolded protein fibrils. Amplification of self-templating amyloid-like fibrils is achieved by the fragmentation of amyloid forms to expose new ends. Breakage of misfolded fibrils also allows the dissemination of self-propagating seeds.

related FALS patients [22,23]. Transgenic mice expressing human SOD1 with a pathogenic mutation very accurately recapitulate common characteristics of ALS such as the selective progressive loss of motor neurons and a progressive loss of motor activity [24]. SOD1-positive inclusions found in human patients and FALS mouse-models show identified granule-coated fibrillar morphologies [25]. Fibrillar protein aggregates that are rich in β-sheet structures act as a structural template to convert normal proteins into a misfolded structure and then elongate the protein fibril. It is not clear if SOD1-containing inclusions of FALS patients are β-sheet rich fibrils, but fibrillar aggregates of the SOD1 mouse model contain amyloid-like aggregates with a β-pleated sheet [26]. Moreover, spinal cord homogenates of transgenic mice expressing the ALS-linked G93A-mutant human SOD1 protein triggered amyloid-like fibril formation of purified wild type and mutant SOD1 protein [27]. Other studies also show that wild type and mutant misfolded SOD1 proteins can induce misfolding of cell-endogenous normal structured wild type SOD1 in a physiological intracellular environment [28]. Glad *et al.* removed misfolded mutant SOD1 proteins using a mutant form specific antibody (GX-CT) in a HEK cell line expressing the SOD1 G127X mutant, but this removal of misfolded seeds did not prevent aggregation of endogenous SOD1 [28]. This result indicates that the newly generated misfolded SOD1 also act as a template for the self-propagation of misfolded SOD1 aggregates.

As mentioned above, many studies suggest that misfolded SOD1-containing fibrils can act as a structural template for a "prion-like replication" from native-structured protein to insoluble misfolded conformers. Misfolded fibrils can be elongated by this conversion process of the normal protein. Breakage of misfolded fibrils is important for this self-propagation process because sheared pieces of misfolded fibrils can be propagated through the template-assisted misfolding of native protein. This self-propagation process is analogous to the replication of infectious prion aggregates (Fig. 1).

Another key feature of prion-like mechanisms is the cell-to-cell spread of misfolded aggregates. Intracellular proteins could be released to the extracellular environment via transport vesicle mediated exocytosis. Another possible process is cell death induced leakage of misfolded seeds. The death of affected cells releases aggregated protein into the extracellular environment, and then neighboring cells can take up these aggregates by phagocytosis (Fig. 2). Progressive neurodegeneration of affected motor neurons is one of the major characteristics of ALS. Therefore, there is a high possibility that seed spreading by cell death is implicated in cell-to-cell transmission of misfolded aggregates. A recent study reported that purified ALS-linked SOD1 mutant aggregates ($SOD1^{H46R}$) effectively penetrate into cells and convert the endogenous wild type SOD1 to misfolded aggregates in the Neuro-2a cell line [16]. These aggregates are continuously released by cells and taken up into neighboring cells via macropinocytosis [16]. These findings indicate that ALS-linked SOD1 aggregates have prion-like properties such as self-perpetuation and the transmission of the misfolded pathological proteins to adjacent cells.

Misfolded aggregate spreading mediated by secreted mutant SOD1 may not be limited to neuron to neuron propagation. It is

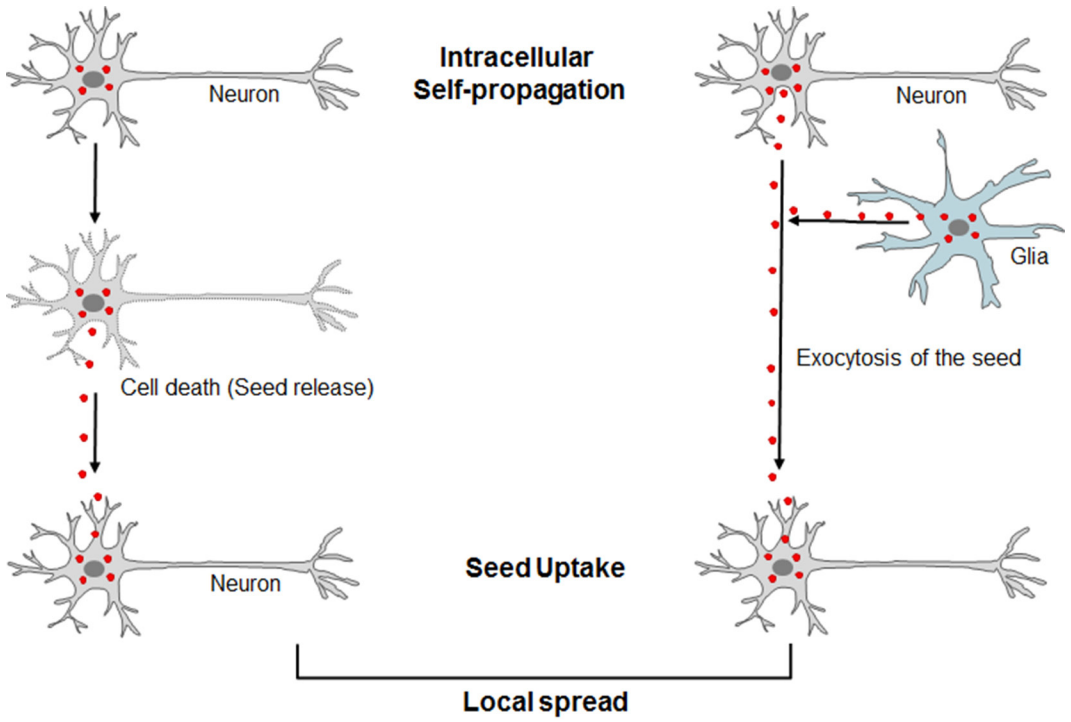

Fig. 2. Putative mechanism of trans-cellular spreading of protein aggregates in ALS. Misfolded protein aggregates are released by cell death or exocytosis. Extracellular seeds can penetrate into neighboring cells and this uptake initiates misfolding and aggregation of native counterparts.

very well accepted that secreted toxic factors produced by glial cells expressing ALS-causing mutant SOD1 induce the loss of motor neurons in the FALS SOD1 mouse model [20]. Using astrocytes derived from neural progenitor cells from the postmortem tissues of ALS patients, Haidet-Phillps *et al.* demonstrated that astrocytes generated from tissues from ALS patients are toxic to motor neurons derived from non-ALS postmortem tissues [29]. Importantly, knock-down of SOD1 in ALS tissue-derived astrocytes was found to mitigate the motor neuron toxicity of these astrocytes [29]. These findings indicate that the generation of a glial cell released factor that is toxic to motor neurons is dependent on the glial SOD1 protein. Furthermore, overexpression of ALS-linked mutant SOD1 in astrocytes induced an increase in exosome release, and those astrocyte-produced exosomes contained mutant SOD1 proteins. Not surprisingly, mutant SOD1 was transmitted to the cytoplasm of spinal neurons through astrocyte-released exosomes [30]. However, additional experimental studies are required to prove that secretory vesicles released from glial cells act as a messenger for misfolded seeding protein.

PRION-LIKE PROPERTIES OF TDP-43 AND FUS

TAR DNA binding protein (TDP-43, 43 KDa) is a highly conserved RNA/DNA binding protein involved in various RNA processing pathways including stress granule formation and RNA splicing [31]. TDP-43 is a major component of pathological inclusions found in spinal cord motor neurons, hippocampal and frontal cortex neurons and glial cells in most SALS and SOD1-negative FALS cases [4]. Under normal conditions, most TDP-43 protein is localized in the nucleus, however, in ALS patients, neurons with cytoplasmic TDP-43 aggregates often showed a corresponding reduction of the nuclear TDP-43 level [32]. Genetic studies have identified *TARDBP* (which encodes TDP-43) mutations in ~4% of FALS cases and a small percentage of SALS cases [6]. Following the identification of *TARDBP* mutations in ALS patients, other FALS mutations were identified in *FUS* which also encodes the RNA binding protein FUS [33]. Intriguingly, FUS and TDP-43 share a very similar domain structure (Fig. 3), and both purified TDP-43 and FUS can easily aggregate *in vitro* [4]. Furthermore, both TDP-43 and FUS contain a prion-like glutamine/asparagine rich domain that shares similarities with yeast prion protein, and this domain is essential for amyloid-like fiber polymerization in cell-free models of RNA granule formation [34].

Like SOD1 proteins, the ALS-causing TDP-43 mutation enhances neurotoxicity and abnormal aggregate formation, and the C-terminal domain is essential for this aggregation process [35,36]. Moreover, almost all ALS linked TDP-43 mutations

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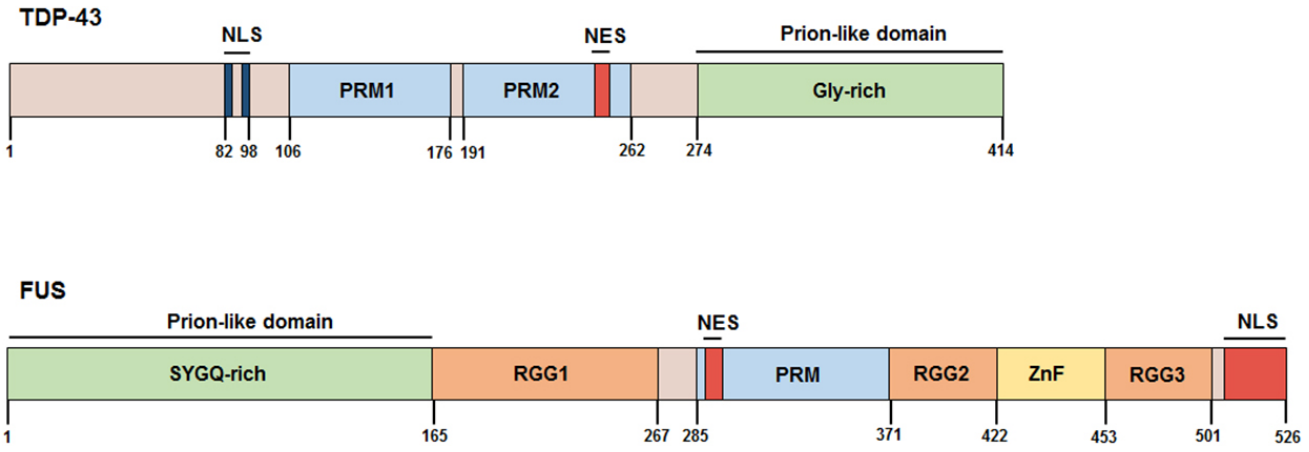

Fig. 3. Schematic representation of the domain structure of TDP-43 and FUS. Different protein domains are indicated in different colors. Both proteins contain prion-like and RRM domains. NLS=Nuclear Localization Signal, RRM=RNA Recognition Motif, NES=Nuclear Export signal, Gly-rich=Glycine rich region, SYGQ-rich=Glutamine/Glycine/Serine/Tyrosine rich region, RGG=Arginine/Glycine rich region, ZnF=Zinc finger motif.

are found in the C-terminal region, and C-terminal truncated fragments of TDP-43 show significantly enhanced aggregation properties *in vitro* and in cells [20]. Taken together, these data suggest that TDP-43 positive neuronal cytoplasmic inclusions are driven by the prion-like C-terminal domain of TDP-43 and that pathologic aggregation process is accelerated by ALS-linked TDP-43 mutations. A recent study reported that the recombinant TDP-43 protein forms sarkosyl-insoluble fibrillar aggregates *in vitro*, and transduction of these TDP-43 fibrils into cultured HEK293T cells overexpressing TDP-43 induces fibrillation of the endogenous TDP-43 [11]. Nonaka *et al.* also demonstrated that the introduction of detergent insoluble TDP-43 aggregates from ALS or FTLD-TDP patients into SH-SY5Y cells expressing TDP-43 induces aggregation of phosphorylated and ubiquitinated TDP-43 in a prion-like, self-templating manner [9]. In addition, phosphorylated TDP-43 aggregates are transmitted between cultured cells, and intracellular TDP-43 aggregates are associated with exosomes [9]. Based upon these results, the prion-like properties of TDP-43 may contribute to the pathological mechanism of ALS.

It remains to be determined whether FUS also shows prion-like propagation, but recent studies have reported that an ALS-causing mutant of FUS forms amyloid-like fibrillar aggregates, and these fibrils act as seeds to trigger the aggregation of wild-type FUS *in vitro* [37].

Accumulating evidence suggests that the prion-like mechanism of TDP-43 and FUS plays an important role in ALS pathogenesis; however, further studies are needed to elucidate their exact mechanism of action and pathological effect.

CONCLUSIONS

The focality of clinical onset and regional spreading of neurodegeneration are typical features of ALS. One of the possible models for the progression of ALS would be the spreading of toxic misfolded seeds from a focal site. If a prion-like mechanism represents key components of disease progression and persistence, antibody-based drug development could be possible. Antibodies could promote break-down of misfolded-aggregates and block their ability to act as a nucleation seed or penetrate into neighboring cells. Interestingly, intracerebroventricular infusion of monoclonal antibodies specific to misfolded SOD1 extends the lifespan of mice with ALS (G93A-SOD1 mouse model) [38].

Another promising therapeutic strategy for ALS involves elucidating the shared pathological mechanism between ALS and Prion diseases. Recent studies indicate that elevation of the eIF2α-phosphorylation level is a common feature of Prion diseases and ALS models [39,40]. Strikingly, downregulation of eIF2α-phosphorylation by PERK inhibitor treatment mitigates the toxicity of Prion proteins and TDP-43 [39,41].

Consequently, dissecting the molecular mechanism of a prion-like process may yield valuable insights into developing therapeutic strategies for ALS. Therefore, lessons and tools from the prion field may become useful for future research on ALS.

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