Dean&Francis
ISSN 2959-409X

Prions and Neurodegenerative Diseases: Mechanisms of Protein Misfolding and Spread

Yichen Mi[1, *]

[1]Southland Christian School, Los Angeles, United States

*Corresponding author: miyichen887@gmail.com

Abstract:

mwymwAbstract:
Prion diseases, also known as transmissible spongiform encephalopathies, are universally lethal neurodegenerative disorders associated with the misfolding of the cellular prion protein into its pathological isoform. This arises through the ability of the misfolded protein to induce conformational changes in normally folded proteins, thereby initiating aggregation processes and neurodegenerative events. Very recent investigations have shown that such prion-like mechanisms are not limited to classic prion diseases but also play a role in the pathogenesis of neurodegenerative diseases (NDDs), including Alzheimer's disease, Parkinson's disease, and Huntington's disease. Protein misfolding, aggregation, and the spreading of such proteins as amyloid-β, tau, and α-synuclein are related to the mechanisms of prion propagation, therefore accelerating disease. This review outlines the molecular pathways underlying prion misfolding, aggregation, and cell-to-cell transmission, focusing on state-of-the-art therapeutic strategies that interfere with these processes. Recent advancements in diagnostic techniques have, in particular, given great boosts to the presymptomatic diagnosis of prion diseases by means of the RT-QuIC assay. It concludes with a discussion of how further research into prion-like mechanisms may provide new therapeutic strategies for a wide array of NDDs.

Keywords: Prions, transmissible spongiform encephalopathies, neurodegeneration, protein misfolding, tau.

1. Introduction

Prion diseases, also known as TSEs, are fatal neurodegenerative disorders associated with a misfolding of the cellular prion protein, PrPC, into its pathological form, PrPSc. Unlike most other proteins, the

ISSN 2959-409X

amazing ability of prions is to force other correctly folded proteins to adopt their misfolded conformation, which results in a self-propagating cascade of protein misfolding. Traditionally, the prion diseases include Creutzfeldt-Jakob disease, kuru, and bovine spongiform encephalopathy-studied in separation from other neurodegenerative disorders. In contrast, recent investigations have pointed to a wider involvement of prion-like phenomena in several other conditions such as Alzheimer‘s disease (AD), Parkinson‘s disease (PD), and amyotrophic lateral sclerosis. The results obtained in this study contributed a lot to the importance of prion biology and gave new insights into the common molecular mechanisms that cause different neurodegeneration [1].

Recent progress in the study of prions has revealed that proteins critical in other neurodegenerative diseases (NDDs)-amyotrophic-β and tau in AD, α-synuclein in PD, and huntingtin in Huntington‘s disease-all possess prion-like properties. In all those instances, the proteins misfold, aggregate, and spread in a cell-to-cell manner somewhat reminiscent of PrPSc transmission. Misfolded proteins can spread either from cell to cell or from one region of the brain to another and contribute to the progression of NDDs. Evidence has now accrued that tau, the other protein involved in AD, is also intracellularly transferable between neurons and thus spreads neurofibrillary tangles in the brain. In a similar vein, alpha-synuclein, which aggregates in brains of patients with PD, can also gain prion-like properties and spread the aggregate distribution to accelerate neurodegenerative processes. This increasing number of studies points out that the spread of misfolded proteins in a prion-like manner is not limited only to classic prion diseases but may well be a common feature among NDDs.

It remains important to realize the mechanisms of misfolding and propagation for prions because potential therapies depend on such knowledge. Misfolding of proteins becomes a key event in the course of NDDs; further on, upon misfolding, such proteins coalesce into toxic oligomers or fibrils disrupting normal cellular functions. Whereas this process culminates in the spongiform degeneration and neuronal death that characterizes the prion diseases, in disorders like AD, PD, and Huntington‘s, similar paths to aggregation are implicated in far-reaching neuronal dysfunction and decline of cognition. How such misfolded proteins spread through the nervous system will be key to determining targets which, when inhibited or slowed, can halt or slow the course of disease. Approaches currently being pursued involve preventing misfolding of proteins, inhibiting aggregation, and blocking cell-to-cell transmission. Such approaches would promise to be very effective in the perspective to slow down the disease progression and amelioration of symptoms in NDDs.

Recent therapeutic strategies have therefore, to date, focused on active vaccinations or elicitation of antibodies that recognize and neutralize the misfolded proteins, thereby blocking their subsequent aggregation and dissemination. Indeed, passive immunotherapy directed against the Aβ and tau proteins has shown limited efficacy in reducing dissemination of these proteins in various models of AD. Similarly, several small molecule inhibitors are currently under study that interfere with protein-protein interactions supporting prion-like transmission. Other strategies involve improving cellular mechanisms that destroy misfolded proteins, including the activation of the ubiquitin-proteasome system or autophagy pathways.

Interest in the prion-like mechanisms of NDDs grew well beyond purely academic relevance, with considerable therapeutic implications for such mechanisms. In summary, targeting early events of protein misfolding and spreading, researchers detail strategies that may prevent or reduce the devastating impact of protein aggregation on brain function. Given the role of misfolded proteins in many neurodegenerative disorders, general therapies directed against prion-like mechanisms might represent a paradigm shift in the way therapeutic intervention is carried out for diseases that, so far, have no cure [2].

This review explains the molecular basis of prion misfolding and spread within NDDs with respect to recent developments, their implications within the field, and potential future directions in therapy. Elucidation of the role of prion-like proteins in the promotion of neurodegeneration is likely to uncover new targets for the treatment of these devastating diseases.

2. History of transmissible spongiform encephalopathies (TSEs)

TSEs, as known as prion diseases, are a group of rare progressive brain degeneration disease with typical pathological profile of sponge-like changes in brain tissues that formation of small holes can be seen under microscope. The TSEs are caused by prions, abnormally misfolded proteins that build up brains. TSEs were first documented in the 18th century due to the observation of scrapie in sheep and goats in the United Kingdom. Many decades later, in the 20th century, considerable work, especially by Stanley Prusiner, unraveled that TSEs are caused by prions-that is, misfolded proteins with the ability to induce conformational changes in normal proteins. This discovery brought about a paradigm shift in the understanding of NDDs and thus implicated prions in diseases such as Creutzfeldt-Jakob Disease (CJD), bovine spongiform en-

cephalopathy-or what is more commonly known as BSE-and Kuru. In humans, TSE diseases include kuru, sporadic and iatrogenic CJD, Gerstmann-Straussler-Scheinker syndrome (GSS), and fatal familial insomnia (FFI). So far, TSE diseases occur only rarely in humans; however, scrapie is a popular problem in sheep, and the recent epidemic of bovine spongiform encephalopathy (BSE or mad cow disease) has profoundly influenced the global cattle industry. Notably, there is strong evidence that many variants of CJD are caused by consuming meat from BSE-infected cows [3].

The various human TSEs, all of which result from a mutation of the prion protein gene on the short arm of chromosome 20, are classified as inherited, infectious or sporadic.

2.1 Inheritable TSEs

2.1.1 GSS

Gerstmann-Sträussler-Scheinker syndrome is a very rare, autosomal dominant prion disease emanating from mutations in the PRNP gene. Clinically, GSS presents with progressive cerebellar ataxia, dysarthria, and cognitive decline, usually starting during mid-adulthood, typically between 35-55 years of age. The illness has a protracted course, measured in several years, with death occurring typically within 5-10 years following symptom onset. GSS is pathologically characterized by diffuse amyloid plaque deposition, made of prion protein, within the central nervous system.

2.1.2 FFI

The FFI is considered a prion disease associated with the particular mutation at codon 178 of the PRNP gene in association with methionine at codon 129. FFI selectively affects the thalamus, manifesting as progressive insomnia, dysautonomia, and motor dysfunction. Sleep disturbance as initial symptom advances to severe insomnia, hallucination, and dementia. The total course of the disease is rapid, which ranges from 7 to 18 months since its onset.

2.1.3 fCJD

Familial Creutzfeldt-Jakob disease is an autosomal dominant disorder that results from mutations in the PRNP gene. It presents with rapid development of dementia, myoclonus, and motor dysfunction, similar to sCJD. However, fCJD has usually been seen to affect people at a younger age, typically in their 40s or 50s, whereas sCJD affects older individuals. The clinical course is usually less rapid compared to sCJD, with survival ranging from 1 to 2 years after symptoms appear.

2.2 Infectious TSEs

2.2.1 Variant creutzfeldt-jakob disease (vCJD)

Variant Creutzfeldt-Jakob disease is an acquired prion disease that has thus far been linked to the ingestion of beef products contaminated with BSE prions. vCJD primarily affects younger patients, with a median age at onset of approximately 28 years, and its clinical presentation often begins with psychiatric and sensory symptoms, which are then followed by progressive ataxia and dementia. The disease course is usually longer compared to sCJD, with a median survival of 12-14 months following symptom onset. Pathologically, vCJD exhibits florid plaques in the brain and accumulation of prions in lymphoid tissues.

2.2.2 Iatrogenic creutzfeldt-jakob disease (iCJD)

The iatrogenic form of the disease is transmitted by contact with infected tissues or via contaminated medical instruments, most frequently by neurosurgical instruments, corneal transplants, dura mater grafts, or through the administration of human-derived growth hormone. The clinical features of iCJD resemble those of sCJD and include rapidly progressive dementia, ataxia, and myoclonus. The latency from exposure to symptom development may range from years to decades, depending on the mode of transmission.

2.3 Sporadic creutzfeldt-jakob disease (sCJD):

Sporadic Creutzfeldt-Jakob disease is the most frequent form of human prion disease. It constitutes 85% of all CJD cases. The etiology of sCJD is still not known, and the disease arises spontaneously. It usually affects people at approximately 60-65 years of age. The disease is typified by rapidly progressive dementia, myoclonus, visual disturbances, and ataxia. Most patients with sCJD die within 6 months to 1 year from the onset of the disease. Neuropathologically, it typically shows spongiform changes, neuronal loss, and deposition of prion protein in the brain [4,5].

3. Mechanism of TSEs

The TSEs consist of a group of fatal NDDs that are caused by the misfolding and aggregation of host-encoded glycoprotein prion protein. Under physiological conditions, the prion protein predominantly adopts an alpha-helical isoform known as PrPC in a protease-sensitive conformation. In disease, the normal isoform of the protein, PrPC, is transformed through a conformational change into an abnormal, protease-resistant isoform now termed PrPSc. This pathological isoform catalyzes the transformation of normal PrPC molecules into PrPSc, which accumulates as

ISSN 2959-409X

insoluble aggregates in the CNS.

In TSEs, the deposition of PrPSc characteristically is associated with a pathognomonic feature: spongiform changes in brain tissue, neuronal vacuolation, glial activation, and amyloid plaque formation. Progressive accumulation of PrPSc is strongly associated with widespread neurodegeneration, synaptic loss, and neuronal apoptosis. Although the exact mechanisms of neurotoxicity induced by PrPSc are unclear, they purportedly include disruption of membrane integrity, calcium dysregulation, and excitotoxicity through the activation of NMDA receptors. Misfolded prion protein aggregates can disrupt intracellular trafficking and contribute to neuronal dysfunction and cell death.

TSEs can also be divided into sporadic, inherited, and infectious forms. The most common form of TSE in humans is the sCJD. An inherited form of TSEs, including familial CJD, GSS, and FFI, results due to mutations in PRNP gene that encodes prion protein. Infectious forms include variant CJD because of exposure to PrPSc through contaminated medical instruments or the ingestion of beef infected with bovine spongiform encephalopathy.

The infectious prion hypothesis, first proposed by Stanley Prusiner, maintains that PrPSc itself constitutes the infectious agent in TSEs-that is, quite a departure from traditional notions of biology as held in respect to the importance of nucleic acids for infectivity. Control efforts are further frustrated by the extreme resistance of PrPSc to inactivation methods such as heat and proteolytic degradation. This unique ability of PrPSc to propagate its abnormal conformation in a template-driven manner underpins the infectious nature of TSEs, though critical gaps remain in understanding the exact molecular mechanisms driving prion replication and neurotoxicity [5-7].

4. Clinical Presentation and Diagnosis

The TSEs represent a group of neuropathic degenerative diseases. Generally speaking, features that include cognitive decline, motor dysfunction, and other neurological disturbances are within the very wide spectrum of clinical manifestations of TSEs. During the course of a TSE illness, patients have manifested symptoms such as the loss of memory, confusion, and behavioral changes. Ataxia, myoclonus, and other movement disorders include motor impairments that occur very frequently. These disorders also exhibit progressive symptoms of severe cognitive impairment, difficulty in speaking, and visual disturbances that eventually lead to coma and death.

Diagnoses depend on the integration of clinical examinations and advanced imaging along with laboratory testing. MRI will essentially help in catching all the typical abnormalities in the brain, including spongiform changes and hyperintensities. The EEG, recording the activities of the brain, would normally reveal the pattern of periodic sharp wave complexes typical in conditions like CJD. CSF examination can be extended for diagnostics through the detection of biomarkers, such as 14-3-3 protein and tau protein, which indicate neuronal damage.

Thus, despite the fact that post-mortem brain biopsy is still considered an absolute gold standard for the confirmation of diagnosis via typical pathological changes, like spongiform degeneration, gliosis, and deposition of misfolded prion proteins, the modern methods significantly enhanced the identification of prions in living patients. RT-QuIC is a very sensitive technique that identifies seeding activity of prions within CSF or other tissues, thus allowing the diagnosis of TSEs much more sensitively and much earlier than that enabled by conventional techniques. These new evolving diagnostic tools increase our capability to find TSEs even in the early stages of disease and help in the management of diseases and potential therapeutic interventions [8,9].

5. Epidemiology of TSEs

Recent findings have established firmly that strong evidence extends the prion-like mechanisms beyond the traditional boundaries of prion diseases to a wide spectrum of NDDs. Many characteristics of aggregation and propagation, similar to those of prion proteins, are shared by misfolded proteins associated with various diseases, including Alzheimer‘s and Parkinson‘s. Tau proteins associated with AD misfolded and then aggregate into neurofibrillary tangles. Recent evidence has supported the concept that tau, like PrPSc in prion diseases, can spread from neuron to neuron and thus spread neurodegenerative pathology through the brain. Tau‘s prion-like properties are part of the neurodegenerative cascade in AD patients initiated by amyloid-β plaques.

The amyloids of misfolded α-synuclein are assembled into Lewy bodies in PD. Similarly to prions, α-synuclein aggregates have also been more recently proven to propagate between cells, thus facilitating the spread of pathology throughout the brain. This mechanism of intercellular protein transfer in PD has been related to the progressive course of motor and cognitive symptoms accompanying the advancement of the disease.

Indeed, research in NDDs, utilizing the concept of prion-like mechanisms, has indeed gained so much knowledge about the spread of misfolded proteins via the nervous system. Indeed, the evidence from in vitro and in vivo experiments did support such proteins causing aggregation in a prion-like fashion, thus making the neurodegenerative research studies shift to analyze the common

pathogenic mechanisms. These investigators target those prion-like features in developing therapeutic methods that would stop the propagation of the misfolded proteins and delay NDD progression of AD and PD [10-12].

6. Conclusion

While studies of TSEs during the last few decades have considerably enlightened the prion hypothesis and the role of misfolded proteins in neurodegenerative phenomena, how prions actually trigger neurodegeneration is still poorly understood. Basic mechanisms of other NDDs in which protein misfolding has been identified to play a key role are also not clear. From continuous research on how the normal prion protein PrPC gets converted into its pathological counterpart PrPSc and through which pathways the spreading and aggregation of prions take place, researchers could achieve more in the treatment of prion diseases and also find their way into treatments of NDDs in general, such as AD and PDs.

The interest in the concept of proteopathic seeding and templated self-assembly of misfolded proteins has been greatly raised by the study of prions, and important insights into other neurodegenerative disorders may quite reasonably emerge. In comparing prion diseases with other neurodegenerative disorders, such as AD and PD, however, one should be very careful due to major gaps in the understanding of the underlying mechanisms. The complex molecular and cellular mechanisms involved in inducing protein misfolding and neurotoxicity by both prion-related and non-prion diseases will become even clearer with continuing investigations.

Future research should go not only toward improving safety procedures for handling prion-infected material but also to cautiously reconsider whether similar precautions might be necessary in handling other NDDs. Empirical research should also be oriented toward explaining in detail the exact mechanisms of nucleation, promotion, and dissemination of proteopathic seeds, outlining above all the ways through which oligomers promote neurodegeneration. In that way, these are challenges to be overcome on the road to great advances in therapy and a deeper understanding of neurodegenerative disorders.

References

[1] Horwich, A. L., Weissman, J. S. Deadly conformations--protein misfolding in prion disease. *Cell*, 1997, 89(4): 499-510.

[2] Prusiner, S. B., et al. Prion protein biology. *Cell*, 1998, 93(3): 337-348.

[3] Van Everbroeck, B., et al. Transmissible spongiform encephalopathies: the story of a pathogenic protein. *Peptides*, 2002, 23(7): 1351-1359.

[4] Oesch, B., et al. Identification of cellular proteins binding to the scrapie prion protein. *Biochemistry*, 1990, 29(24): 5848-5855.

[5] Scallet, A. C., Carp, R. I., Ye, X. Pathophysiology of transmissible spongiform encephalopathies. *Current Medicinal Chemistry - Immunology, Endocrine & Metabolic Agents*, 2003, 3(2).

[6] DeArmond, S. J., Prusiner, S. B. Etiology and pathogenesis of prion diseases. *The American Journal of Pathology*, 1995, 146(4): 785-811.

[7] Joshi, T., Ahuja, N. The prion basis of progressive neurodegenerative disorders. *Interdisciplinary Perspectives on Infectious Diseases*, 2023.

[8] Caughey, B., Chesebro, B. Prion protein and the transmissible spongiform encephalopathies. *Trends in Cell Biology*, 1997, 7(2): 56-62.

[9] Hernaiz, A., Toivonen, J. M., Bolea, R., Martín-Burriel, I. Epigenetic changes in prion and prion-like neurodegenerative diseases: recent advances, potential as biomarkers, and future perspectives. *International Journal of Molecular Sciences*, 2022, 23(20): 12609.

[10] Jaunmuktane, Z., Brandner, S. Invited review: The role of prion-like mechanisms in neurodegenerative diseases. *Neuropathology and Applied Neurobiology*, 2020, 46(6).

[11] Song, Z., et al. Molecular mechanisms of neurodegeneration mediated by dysfunctional subcellular organelles in transmissible spongiform encephalopathies. *Acta Biochimica et Biophysica Sinica*, 2013, 45(6): 452-464.

[12] Kraus, A., et al. High-resolution structure and strain comparison of infectious mammalian prions. *Molecular Cell*, 2021, 81(21): 4540-4551.e6.