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Neurodegenerative Disorders and Prionopathies

Jin Jun Luo[1,2] and Nae J Dun[2]

[1]Departments of Neurology, Temple University School of Medicine, Philadelphia, USA
[2]Departments of Pharmacology, Temple University School of Medicine, Philadelphia, USA

Neurodegenerative disorders are a group of progressively worsening neurological disorders caused by neuronal degeneration in the brain. Depending on the location, degeneration in the cerebral cortex causes dementia including Alzheimer's disease (AD), Pick's disease (PiD), and diffuse Lewy Body dementia (DLBD). In the basal ganglia, brainstem and cerebellum, degeneration causes Parkinson's disease (PD), Huntington's disease (HD), multisystem atrophy (MSA), dentatorubropallidoluysian atrophy, Freidreich's ataxia, multiple system atrophy, and types 1, 2, 3, 6, 7 spinocerebellar ataxia. Degeneration that involves only motor neurons causes amyotrophic lateral sclerosis (ALS), familial spastic paraparesis, spinal muscular atrophy, spinal and bulbar muscular atrophy.

Prion diseases, also called TSE (transmissible spongiform encephalopathies), are a rare group of fatal neurodegenerative disorders affecting humans and animals. In humans, prion diseases include Creutzfeldt - Jakob disease (CJD), Variant Creutzfeldt-Jakob disease (vCJD), Gerstmann-Straussler-Scheinker syndrome, fatal familial insomnia and Kuru disease. Prion diseases can be sporadic, inherited or familial, iatrogenic, and variant forms. The most common prion disease is sporadic CJD, which is characterized by dementia, ataxia and myoclonus, and, pathologically, amyloid deposits composed of mainly prion proteins [1].

Since established two decades ago, the concept of prion disease has significantly impacted both the basic neuropathological research and clinical neurology practice. Prions, as a group of infectious self-reproducing pathogens, comprise a protein that resists inactivation by procedures that modify nucleic acid [2]. Dr. Stanley B. Prusiner discovered prions in 1982 at the University of California, San Francisco and his work lead to the 1997 Nobel Prize in physiology.

Prions are produced by recruiting the normal cellular isoform of the prion protein PrP^{c} and stimulating its conversion into the disease-causing isoform PrP^{sc}. The normal isoform PrP^{c} is a glycoprotein containing 208 amino acids derived from a precursor PrP of 253 amino acids. PrP^{c} comprises approximate 45% α-helical with only two very short stretches of β-sheet, while PrP^{sc} has less than 30% α-helix and approximate 45% β-sheet [3]. PrP^{c} is tethered to the cell surface via a glycosyl phosphatidyl inositol (GPI) anchor at the protein's C terminus [4]. Under physiological conditions, PrP^{c} folds into its characteristic and functional three-dimensional structure, despite the fact that its physiologic roles remain unknown. The misfolded PrP^{sc} is the main pathological component of the β-sheet febrils in prion diseases. There are two models to explain the conformational conversion of PrP^{c} into PrP^{sc}: the "template-directed refolding" and the "seeded nucleation" hypotheses. The former hypothesis predicates a role for PrP^{sc} on PrP^{c}. A single PrP^{sc} molecule binds to a single PrP^{c} molecule and catalyzes its conversion into PrP^{sc}. The two PrP^{sc} molecules then come apart and can go on to convert more PrP^{c} [5]. In the "seeded nucleation" hypothesis, the infectious agent would consist of a highly ordered aggregate of PrP^{sc} molecules. The aggregated state is the fundamental property of infectivity [6-8].

Prion diseases are transmissible because inoculation or transplantation of the diseased brain or non-brain tissue in humans and animals has reproduced prion diseases [9,10]. Notably, CJD has also been observed in recipients of human organ transplantations and in cannibals [9,10], though it may require a long incubation time to develop the disease. For example, a particular pattern at 10-19 years' incubation latency was observed in surgical transmission of CJD [11]. Transmission of prions from animals to humans, such as mad cow disease, is believed to have caused more than 200 cases of vCJD [12]. Pathologically, prion diseases cause spongiosis, neuronal loss, astrogliosis, and accumulation of misfolded PrP^{sc}. Prion diseases are characterized by widespread neurodegeneration.

Robust evidence from basic and clinical studies has revealed that many similarities are shared in neurodegenerative disorders, including prion diseases, at many different levels ranging from molecular to systemic. Clinical observations in general showed that the majority of those diseases are sporadic, while only approximately 10% familial forms [13]. The onset of symptoms is commonly in late adult life instead of youth even in the inherited forms. The pathologic findings showed abnormal accumulations of extracellular or intracellular fibrils and/or inclusions suggestive of the presence of a misassembling or misfolding protein. Misassembled or misfolded proteins aggregate and form fibrils and/or inclusions are seen in the brains of patients with AD, DLBD, PD, PiD, MSA, and ALS, and PrP^{sc} in CJD. Laboratory findings disclosed that abnormal aggregations may interfere with neuronal functions including axonal transport, membrane integrity, intracellular signal transduction, mitochondrial function, and eventually cause programmed cell death [8,9,14-16].

Recent studies showed that the pathology of AD, PD and ALS can be transmitted to animals in a way similar to that by which a prion disease was transmitted with PrP inoculation. For example, amyloid-(Aβ) peptide induced aggregation occurred in transgenic mice or primates after injection of AD brain extracts or purified and synthetic Aβ peptides [17-19]. Intraperitoneal injection of mouse brain extracts containing Aβ aggregates or tau protein resulted in amyloid deposition and other pathological alterations in the recipient mice [9,20]. Injection of synthetic oligomeric mouse α-synuclein, a pathologic protein in PD, into the substantia nigra of wild-type mice, induced spreading of α-synuclein throughout the brain and recapitulated the Parkinsonian phenotype, losing dopaminergic nigral neurons, reducing striatal dopamine levels and resulting in motor deficits [21]. Inclusion formation and neuronal cell death through neuron-to-neuron transmission of

***Corresponding author:** Dr. J.J. Luo, Departments of Neurology and Pharmacology, Temple University School of Medicine, 3401 North Broad Street, Suite C525, Philadelphia, PA 19140, USA, Tel: 1-215-707-3040; Fax: 1-215-707-8235; E-mail: jluo@temple.edu

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α-synuclein was demonstrated in vitro and in vivo models for PD [22,23]. Changes in levels of enkephalin in the amygdala and globus pallidus were observed in the injected mice, reflecting neuronal dysfunction resulting from aggregate pathology [24]. Interestingly, α-synuclein inclusions found in the submucosal Meissner plexus of the enteric nervous system [25] can be transmitted to the CNS via vagus nerves [26], and subsequently, activate intracellular α-synuclein-associated Lewy body pathology in PD [27]. Importantly, neurological disorders can be produced by either peripheral (extracerebral) or direct brain (intracerebral) inoculation [22,23]. Those findings provide evidence of cell-to-cell spread of pathologic proteins of neurological disorders in animals, suggesting those pathological proteins may have seeding abilities, like prion diseases, to transmit pathology [17,28].

To date, there is no direct evidence in humans indicating that the diseases caused by misfolded Aβ, tau, α-synuclein are infectious. However, the possibility that the neurodegenerative disorders might be transmitted from person to person may not be balderdash. For example, a prion may be taken up by dendritic cells through the skin [9,29]. In prion diseases, PrP^{sc} and its infectivity levels do not always correlate well. The presence of little or no PrP^{sc} in brain tissue may still have high levels of infectivity [30,31] and peripheral tissue may have, sometimes even higher, infectivity [32]. Clinically, a familial form of prion disease can manifest a neurological disorder, such as AD, with the presentations of typical pathology and clinical phenotype [33].

The discovery of a possible prion-like infection mechanism in neurological diseases such as AD and PD would significantly influence the direction of research on the pathogenesis of these neurodegenerative disorders, and would be a significant step towards developing effective therapeutic approaches, as the current treatments have been disappointing. If proven to be correct, the concept of prionopathies for neurodegenerative disorders may significantly impact clinical practice.

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