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Biology and Genetics of Prions Causing Neurodegeneration

Stanley B. Prusiner
Institute for Neurodegenerative Diseases and Department of Neurology, University of California, San Francisco, California

Stanley B. Prusiner: stanley@ind.ucsf.edu

Abstract

Prions are proteins that acquire alternative conformations that become self-propagating. Transformation of proteins into prions is generally accompanied by an increase in β-sheet structure and a propensity to aggregate into oligomers. Some prions are beneficial and perform cellular functions, whereas others cause neurodegeneration. In mammals, more than a dozen proteins that become prions have been identified and a similar number has been found in fungi. In both mammals and fungi, variations in the prion conformation encipher the biological properties of distinct prion strains. Increasing evidence argues that prions cause many neurodegenerative diseases (NDs), including Alzheimer's, Parkinson's, Creutzfeldt-Jakob, and Lou Gehrig's diseases, as well as the tauopathies. The majority of NDs are sporadic, and 10% to 20% are inherited. The late onset of heritable NDs, like their sporadic counterparts, may reflect the stochastic nature of prion formation; the pathogenesis of such illnesses seems to require prion accumulation to exceed some critical threshold before neurological dysfunction manifests.

PRION, NEURODEGENERATION: INTRODUCTION

Most neurodegenerative diseases (NDs) are age-dependent, i.e., their incidence increases with advancing age. An expanding body of evidence argues that many different NDs are caused by prions, which are formed from normal proteins (146). Prions arise when normal proteins acquire an alternative conformation that becomes self-propagating. The most well-studied mammalian prions are composed of PrP^{Sc} proteins that cause Creutzfeldt-Jakob disease (CJD) in humans, scrapie in sheep, chronic wasting disease (CWD) in deer and elk, and mad cow disease. Conformational variants of PrP^{Sc} create different regional patterns of PrP accumulation and thus produce different disease phenotypes. Ten to twenty percent of CJD patients have a familial form of the disease due to mutations in the *PRNP* gene that encodes PrP^{C}. Prions composed of PrP^{Sc} are formed from PrP^{C} by a posttranslational process that results in a profound change in conformation. In some CJD patients, PrP^{Sc} and smaller fragments are found in amyloid plaques. Although the number of prions identified in mammals and in fungi continues to expand, the existence of prions in other phylogeny remains undetermined. Some mammalian prions perform vital functions and do not cause

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disease; such nonpathogenic prions include cytoplasmic polyadenylation element binding (CPEB) protein, mitochondrial antiviral-signaling (MAVS) protein, and T-cell-restricted intracellular antigen 1 (TIA-1). The pathogenic mammalian prions include PrP (prion protein), Aβ, tau, α-synuclein, superoxide dismutase 1 (SOD1), and possibly huntingtin, each of which causes a distinct ND (Table 1). All mammalian prion proteins adopt a β-sheet-rich conformation and appear to readily oligomerize as this process becomes self-propagating (Figure 1). Control of the self-propagating state of benign mammalian prions is not well understood but is critical for the well-being of the host. In contrast, pathogenic mammalian prions appear to multiply exponentially, but the mechanisms by which they cause disease are poorly defined. We do not know if prions multiply as monomers or as oligomers; notably, the ionizing radiation target size of PrP^{Sc} prions seems to suggest it is a PrP trimer (5). The oligomeric states of pathogenic mammalian prions are thought to be the toxic forms, and assembly into larger polymers, such as amyloid fibrils, seems to be a mechanism for minimizing toxicity. To date, there is not a single medication that halts or even slows one ND caused by prions. This may reflect the unprecedented pathogenic mechanisms that feature in each of the prion diseases and highlights the urgent need to develop informative molecular diagnostics and effective antiprion therapeutics.

MAMMALIAN PRIONS

Discovery of Prions

Following the experimental transmission of the human disorders kuru and CJD to apes and monkeys, the search intensified for a slow-acting virus that causes the analogous disease, called scrapie, in sheep and goats (42, 43, 48, 63). As preparations from the brains of scrapie-infected hamsters were enriched for infectivity, evidence for an essential protein emerged, but no similar data for a nucleic acid could be generated. To the consternation of many, I introduced the term prion in order to distinguish from viruses the proteinaceous infectious particles causing scrapie and CJD (142). Despite numerous attempts to demonstrate a scrapie-specific nucleic acid, none could be found, and as such, those investigations were eventually abandoned (162).

Soon after the introduction of the prion concept, a protein with a molecular weight of 27–30 kDa was found in purified fractions containing high levels of scrapie infectivity (9, 119). This protein was designated prion protein 27–30 (PrP 27–30). Scrapie infectivity and PrP 27–30 were found at the top of sucrose gradients, indicating some of the infectivity was likely to be very small, in agreement with the small ionizing radiation target size, whereas the majority of the infectivity sedimented to the bottom (1, 5, 148, 149). The rod-shaped structures at the bottom of the gradients were shown to be composed of PrP 27–30 and to stain with Congo red dye, establishing that these large aggregates were amyloid (150). This discovery suggested that amyloid deposits in other disorders, such as Alzheimer's (AD) and Parkinson's diseases (PD), might be composed of causative proteins, i.e., prions (143).

Plaques, Tangles, and Inclusions

Beginning in the mid-1980s, the proteins in plaques, tangles, and intracellular bodies of the brains of patients who died of neurodegeneration were identified through purification or

immunostaining (14, 54, 61, 98, 173, 200). Each of these proteins was found to aggregate into fibrils under some conditions and to form amyloids (Figure 1). The amyloid fibrils in AD were found to contain the Aβ peptide (53, 116), which is cut from the larger amyloid precursor protein (APP). Neurofibrillary tangles (NFTs) in many NDs were found to contain the tau protein. Those same proteins were also identified when genetic studies found that specific mutant genes cause familial forms of neurodegeneration (55, 77, 83, 140). Subsequently, expression of these mutant genes in transgenic (Tg) mice was shown to recapitulate many aspects of the human illnesses (for review, see Reference 145).

Despite these similarities with CJD, many investigators still prefer to think about the other NDs as unrelated because Gajdusek, Gibbs, and their collaborators were unable to transmit AD and several other NDs to apes and monkeys (56, 57). These initial attempts to demonstrate transmissibility of AD and PD to apes and monkeys were made long before the Aβ peptide and α-synuclein, the respective causative proteins, were isolated, so neither could be used as biomarkers. Later, Ridley, Baker, and colleagues demonstrated transmission of disease to marmosets, as indicated by Aβ cerebral amyloidosis, after intracerebral injections of AD brain homogenates (3, 157). The incubation times in those studies exceeded 3.5 years, making confirmation of such experiments impractical. Later, Tg mouse studies would supplant the use of nonhuman primates.

Inherited Neurodegenerative Diseases

The recognition that 10% to 20% of CJD cases occur in families led to the suspicion that heredity might play a role in the pathogenesis of this disorder (Table 1). Subsequently, transmission of familial (f) CJD and Gerstmann-Sträussler-Scheinker disease (GSS) to apes and monkeys was reported, but multiple explanations involving slow viral illnesses in families were offered (115, 160). First, the putative CJD virus might be passed from mother to offspring during childbirth as was later shown for HIV. Second, the CJD virus might be passed to offspring *in utero* or during childhood when parents and children lived in close proximity. A third possibility was that a chromosomal gene conferred susceptibility to a ubiquitous CJD virus. All three of these explanations proved incorrect.

The identification of a mutation followed by the demonstration of genetic linkage in GSS patients was first reported for the P102L mutation in the PrP gene (77). Subsequently, four more mutations in the PrP gene were linked to fCJD, fatal familial insomnia (FFI), and GSS with NFTs (32, 41, 122, 141). More than 40 different mutations of the PrP gene have been identified, of which 35 are point mutations and the remainder are octapeptide expansions or deletions (see References 95, 121, 190). Virtually all cases of GSS and FFI appear to be caused by germ line mutations in the PrP gene. Some mutations seem to have arisen de novo; whether any of these mutations in PrP are responsible for the development of PrP prion disease remains to be established.

For years, the late-onset presentation of fCJD and GSS presented a conundrum. Despite mutations in PrP being expressed early in life, such prions do not cause disease for decades. In studies of fCJD caused by the E200K mutation in PrP, actuarial analyses showed that if carriers live long enough, they would all develop CJD, i.e., there was complete penetrance (18, 174).

Analogous to discoveries coming from GSS and fCJD, mutant proteins causing other inherited NDs were determined to be the same as those found in disease-specific amyloid deposits within intracellular inclusions, such as NFTs or Lewy bodies, or outside of cells as plaques (for review, see Reference 145). These parallel findings offered support to the early proposal that such common diseases as AD and PD might be caused by prions (143).

Late-Onset Neurodegeneration

Despite the fact that most mutant proteins that cause familial NDs are expressed early in embryogenesis, signs of neurological dysfunction are generally delayed for decades. This finding argues that some event occurs with aging that renders a disease-specific protein pathogenic. Many explanations have been offered to explain the late onset of familial NDs (Table 2), including age-dependent mitochondrial DNA mutations; oxidative modifications of DNA and proteins; proteasome malfunction; diminished innate immunity; exogenous toxins, such as alcohol and drugs; concomitant conditions, such as atherosclerosis; somatic mutations; chaperone malfunction; haploinsufficiency; RNA-DNA differences; expanded repeat segments in proteins and noncoding regions of DNA; and postinfectious syndromes. However, little evidence supports most of these proposed mechanisms. The formation of prions from etiologic proteins provides a plausible explanation for the late-onset presentations of many different NDs and is consistent with the observation that aging appears to be the most important risk factor. These proteins must first refold into prions and then accumulate in sufficient numbers for an infection to become self-sustaining (146). Presumably, the number of prions being generated by this self-propagating process has to reach a threshold before an infection can continue unabated (144). Under these conditions, prion propagation becomes uncontrolled, and eventually central nervous system (CNS) dysfunction results.

One fascinating insight into the control of the timing of disease onset comes from studies of ~35 fCJD families with expanded PrP octarepeat regions (27, 177). Wild-type PrP^{C} contains four octarepeats; one to four additional octarepeats cause late-onset fCJD with a mean age of 62 years, and —five to eight additional octarepeats cause early-onset fCJD or GSS with a mean age of 32 years. In other words, the fifth additional octarepeat decreases the age of disease onset by three decades. This profound transition in pathogenesis was found to correlate with a shift in Cu^{2+} binding to PrP: a high Cu^{2+} occupancy state shifted to a low one (177). Titrations showed that one Cu^{2+} ion binds to each histidine in the high occupancy state; each of the four octarepeats contains a single histidine. In the low occupancy state, a single Cu^{2+} ion coordinated with four histidines. The mechanism by which Cu^{2+} ions that are bound to mutant PrP with octarepeat expansions participate in the formation of PrP^{Sc} remains unknown. Whatever the process that controls the formation of prions in the inherited PrP prion diseases, it may prove relevant to some other age-dependent NDs.

Sporadic Neurodegenerative Diseases

In the absence of a mutation or an environmental cause, such as an infection or a toxin, the NDs are generally referred to as sporadic. Such illnesses are thought to arise stochastically. Although 10% to 20% of cases are inherited, more than 80% are sporadic. This relationship has been found for CJD, AD, PD, the tauopathies, and amyotrophic lateral sclerosis (ALS)

but not for Huntington's disease (HD), which is always inherited (183). Notably, inheritance of the *e4* allele of apolipoprotein E is the only well-established genetic risk factor for sporadic AD (69, 112). Presumably, many disease-causing proteins can form prions but most are cleared before they begin to multiply in sufficient numbers to support a sustained infection involving spread to adjacent cells and eventually other regions of the brain. One possible mechanism to explain sporadic prion diseases involves precursor proteins becoming transformed into disease-causing prions through a stochastic process, which most of the time probably represents a dead-end route in which small numbers of prions are cleared via protein degradation pathways.

PrP Prions

Synthetic PrP prions provided indisputable evidence that the disease-causing agent of CJD and other PrP prion diseases is composed solely of protein (23, 45, 102, 114, 193). The first glimmer of a synthetic PrP^{Sc} prion came when we produced a synthetic PrP peptide of fifty-five amino acids containing the P101L mutation (mouse numbering) that causes GSS in humans; the peptide was made by coupling individual amino acids together, as was later done for the synthetic Aβ peptide (90). After we mixed the PrP peptide with acetonitrile, which caused it to adopt β-sheet-rich structure, the peptide was injected into a Tg mouse model of GSS (80, 81, 187). Approximately a year later, the inoculated mice became ill, whereas the uninoculated ones remained well for another six months. Some investigators have argued that the subsequent illness in the uninoculated controls showed that the peptide was not a prion but was merely an accelerator of disease. Such arguments persisted for a more than a decade (130). Importantly, we were able to show by serial passage that the brains of the inoculated mice contained a transmissible entity, i.e., a prion (187).

In part on the basis of studies in yeast (172), we assembled recombinant mouse PrP(89–230) made in bacteria into amyloid fibrils and injected them into Tg mice expressing the same N-terminally truncated PrP. When the mice remained well for more than 250 days, we concluded that the experiment was negative and wrote a paper about our experience (4). Unintentionally, the experiment was not terminated and approximately 600 days after inoculation, the mice showed signs of neurological dysfunction and their brains showed the hallmarks of prion disease on neuropathological examination (102). The prion strain found in these mice was more resistant to denaturation at higher concentrations of GdnHCl than that generally seen with naturally occurring strains of prions (103).

When we examined the stability of a half-dozen prion isolates in mice, including one of the synthetic prions, we found that the more stable strains, which resisted denaturation, produced longer incubation times, and the less stable ones yielded shorter incubation times (104). On the basis of this finding, we produced synthetic prions under conditions that created PrP preparations that were highly resistant to denaturation as well as those that were quite susceptible and those that were intermediate. The stable preparations produced long incubation times, whereas the more labile ones yielded much shorter incubation times (23, 45). Although these investigations confirmed and extended our earlier work, they remained very expensive because the incubation times exceeded 500 days on first passage. More extensive analyses in cell culture and Tg mice have demonstrated the evolution of prions

toward strains causing shorter incubation times and harboring an unglycosylated, protease-resistant PrP^{Sc} fragment (PrP 27–30) of 21 kDa (45, 46, 105).

Aβ Prions

In a series of incisive experiments, Mathias Jucker and Lary Walker collaborated on the transmission of Aβ prions to weanling Tg(APP23) mice expressing mutant human APP. Much of their work was performed with brain homogenates from aged Tg(APP23) mice that spontaneously develop Aβ amyloid plaques. The inoculum prepared from these old mice dramatically accelerated the deposition of nascent Aβ amyloid, and immunoabsorption of Aβ in the inoculum prevented the accelerated deposition of Aβ (123). These investigators also reported transmission of Aβ prions after intraperitoneal injections (35). More recently, Claudio Soto and colleagues, as well as Jucker and Walker, reported that brain homogenates from AD patients could also transmit disease to Tg mice expressing wild-type human APP and Tg rats expressing mutant APP, neither of which develops cerebral Aβ deposits spontaneously (126, 161).

Using bigenic mice expressing mutant APP and luciferase under the control of the murine *Thy-1.2* and *Gfap* promoters, respectively, my colleagues and I found brain homogenates from aged Tg(APP23) mice transmitted Aβ prions, as reflected by increased bioluminescence and Aβ deposits (194). Subsequently, we found that fractions highly enriched for Aβ produced an increase in bioluminescence after approximately five months, which was approximately six weeks more rapid than that seen with the crude brain homogenates. Most important, synthetic Aβ peptides became prions during polymerization into amyloid, establishing that some hypothetical contaminate was not responsible for the change in bioluminescence (178).

Remarkably, Heiko Braak not only described the spreading of Aβ amyloid plaques but also showed the concurrent deposition of NFTs composed of the tau protein in the brains of autopsied AD patients (11, 12). Recent studies have traced the spread of tau prions using functional magnetic resonance imaging (fMRI) intrinsic connectivity analysis (202). Such spreading of prions was described much earlier for scrapie prions in ovines and rodents (38, 39, 64, 92, 165, 181, 182).

Familial Alzheimer's Disease

Soon after the identification of mutant PrP genes, missense mutations in the *APP* gene were discovered in familial AD (fAD) followed by mutations in the presenilin 1 and 2 genes (*PS1* and *PS2*) encoding the catalytic subunits of γ-secretase; these mutations result in elevated levels of wild-type Aβ peptide (Table 1) (55, 68, 163, 164, 175, 176). In addition, more than a dozen mutations within the Aβ peptide have been discovered (6, 192), most of which also cause fAD. All of the mutations causing fAD, which account for 10% to 20% of AD cases, are autosomal dominant and produce one or two amino acid substitutions.

In contrast to APP mutations causing fAD, the A673T mutation in APP identified in a genome-wide study of Icelandic people seems to protect against late-onset AD (88). This missense mutation is located at the β-secretase cleavage site and presumably inhibits the

production of the Aβ peptide. Diminished wild-type Aβ levels would seem likely to reduce the chances of sustained Aβ prion formation.

Although no authentic animal models of AD exist, much has been learned from mice, and more recently Tg rats (22), that express mutant human APP transgenes. The initial Tg mouse models of fAD used human APP harboring mutations that elevate the level of wild-type Aβ (44, 78); these mice exhibited numerous amyloid plaques filled with fibrils composed of the Aβ peptide as well as astrocytic gliosis and behavioral changes. Mice were constructed expressing mutant human APP, presenilin, and tau in the hope of building a more authentic model of AD; these mice were designated triple Tgs, or 3×Tg-AD, mice (131). Such Tg models have been used to assess the therapeutic efficacy of antibodies for the clearance of the Aβ peptide (29). Unfortunately, attempts to treat AD patients with anti-Aβ antibodies have yet to produce an FDA-approved therapy (167).

Tau Prions

The tauopathies sit at an interface between psychiatry and neurology. These disorders often present after age 40 as psychiatric illnesses. Often, psychiatrists see patients with frontotemporal dementia (FTD) for several years before they refer them to neurologists with the diagnosis of AD. Tau lesions in the frontal lobes can produce behavioral disinhibition, apathy, inappropriate social interactions, depression, and insomnia as well as reduced executive function (152). Later, semantic dementia, drug abuse, alcoholism, and sometimes suicide are seen. As behavioral and language problems worsen, these inherited and sporadic neurological disorders are frequently classified clinically as behavioral variants of FTD (bvFTD). Different phenotypes of tauopathy, including progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and Pick's disease, may be due to conformational variants of tau prions producing lesions in different neuronal circuits (166).

In an important series of studies over the past four decades, contact sport athletes, including boxers and football and hockey players, have symptoms similar to those of FTD patients. Numerous NFTs have been found in the frontal lobes of contact sports athletes (24), some of whom have committed suicide. The first football player identified with a tauopathy was the Pittsburgh Steeler Mike Webster, who played professional football for 16 seasons and died at age 50 (136). Subsequently, fifty other football players in high school, college, and the NFL who committed suicide were identified with tauopathies (118). Recently, a 27-year-old Marine, who suffered multiple episodes of traumatic brain injury (TBI) during explosions of roadside bombs in Iraq, was found to suffer from a tauopathy. Following the diagnosis of posttraumatic stress disorder (PTSD), he was honorably discharged, divorced his wife, and became an alcoholic. Eight months after his honorable discharge, he committed suicide by hanging; at autopsy, numerous NFTs were found in his frontal lobes (135). Many similar cases of military veterans with the symptoms of PTSD have been reported (118).

US Army studies show that multiple episodes of mild TBIs from exposure to blasts from improvised explosive devices increase the risk for PTSD (73). The latest estimates suggest that ~450,000 men of the 2 million who have served in Iraq or Afghanistan will develop PTSD. How many of these will develop a posttraumatic tauopathy [or chronic traumatic encephalopathy (CTE)] caused by tau prions is unknown. Although concussive forces

presumably stimulate tau prion formation in the human brain, the mechanism by which this occurs remains unknown.

Aggregates formed from truncated recombinant human tau composed of residues 242–364 (K18 fragment) in the presence of arachidonic acid were shown to enter C17 cells and seed the polymerization of endogenous tau (40). These studies were extended using HEK293 cells expressing full-length wild-type human tau(2N4R) as well as truncated and mutant human tau(P301S) (62, 91). Michel Goedert, Markus Tolnay, and their colleagues described the transmission of mutant tau(P301S) prions produced in Tg mice to recipient mice expressing wild-type human tau (21). After approximately six months, the inoculated Tg mice showed wild-type tau aggregates that had spread from the site of inoculation to neighboring regions. Synthetic tau fibrils were formed from full-length tau(2N4R) with the P301S mutation and from the truncated K18 fragment with the P301L mutation expressed in *Escherichia coli*, which were purified and polymerized into fibrils in the presence of heparin. The fibrils were inoculated intracerebrally into young Tg(*MAPT**P301S) mice overexpressing mutant human tau (84). These inoculations produced NFT-like inclusions that propagated from injected sites to connected brain regions in a time-dependent manner. Interestingly, injection of the tau fibrils into either the hippocampus or the striatum, along with the overlaying cortex, gave rise to a distinct pattern of spreading. Unlike tau pathology that spontaneously develops in older Tg(*MAPT**P301S) mice, the tau deposits resembled NFTs as reflected by their acetylation, thioflavin S positivity, and resistance to limited proteinase K digestion.

As with the Aβ amyloid plaques of AD, the NFTs also spread along defined neuroanatomical pathways (10). Presumably, the tau prions spread transsynaptically as they move from one neuron to another. Recent Tg mouse models expressing human tau in the entorhinal cortex show spread along neuroanatomically defined pathways to hippocampal pyramidal neurons, especially in CA1 and dentate gyrus granule cells (28, 108, 139).

Inherited Tauopathies

Familial forms of FTDs result from mutations in the *MAPT* gene that encodes the tau protein; these disorders include PSP, Pick's disease, frontotemporal lobar degeneration (FTLD), CBDs, and argyrophilic grain disease (AGD) (Table 3). FTD with parkinsonism has been linked to mutations in the *MAPT* gene on chromosome 17 and is often referred to as FTDP-17, in which behavioral and personality changes, cognitive impairment, and signs of motor dysfunction are present. In addition to the gene encoding tau, mutations in other genes encoding TDP43, FUS, UPS, progranulin, and C9orf72 have been linked to familial forms of the FTDs. As with CJD and AD, familial FTDs account for 10% to 20% of FTD cases. Most of the FTD cases appear to be sporadic, seem likely to occur spontaneously, and are likely to be caused by tau prions or other prions formed from TDP43 or FUS. Both progranulin and C9orf72 are thought to cause disease through haploinsufficiency (127, 153). Interestingly, the expanded hexanucleotide repeat upstream of the C9orf72 coding region appears to encode several dipeptides that are translated into proteins, which deposit as neuronal cytoplasmic inclusions, suggesting an alternative pathogenic mechanism.

In the FTDs caused by tau prions, NFTs are the neuropathological hallmark of these illnesses. Finding NFTs composed of tau fibrils in many CNS disorders led to the conclusion that tangles are nonspecific, unimportant histopathological entities. The discovery of mutations in the tau gene in patients suffering from familial FTDs brought remarkable clarity to a once rather Byzantine area of neurology (75, 83, 154). As with PrP^{Sc}, conformational variants of tau prions are strains that create different regional patterns of tau accumulation. These distinct patterns of tau prion accumulation produce different disease phenotypes.

The primary tauopathies encompass both the familial and sporadic forms of the FTDs, in which pathologic deposits of tau accumulate as either NFTs or collections of fibrils within neurons. In contrast, the secondary tauopathies have many causes, the most common of which is AD. Importantly, ablation of the *MAPT* gene encoding tau ameliorated disease in AD mouse models expressing mutant APP (158). Other disorders in which tau-laden NFTs accumulate include viral illnesses, such as rabies, subacute sclerosing panencephalitis, and postencephalitic PD; inherited disorders such as Nieman-Pick disease and myotonic dystrophy; and a disease of unknown etiology called Guam ALS-PD with dementia. In addition, the F198S point mutation and an octarepeat expansion in PrP have been reported to cause GSS and fCJD with NFTs, respectively (79, 99).

Synuclein Prions

In the late 1990s, fetal brain cells taken from the substantia nigra of aborted fetuses were transplanted into patients with advanced PD to mitigate the loss of dopaminergic neurons. A decade later, Lewy bodies were found in the grafted fetal brain cells when the PD patients died (97, 106). The surface of a Lewy body is covered with fibrils composed of β-sheet-rich, α-synuclein proteins. The normal form of α-synuclein seems to be either unstructured or high in α-helical structure, but like other prion precursor proteins, α-synuclein can adopt a β-sheet-rich conformation. Although unproven, it seems likely that β-sheet-rich α-synuclein prions crossed from the patient's own neurons into the grafted cells and induced a change in the structure of α-synuclein (134). Once established, this process became self-propagating, as is the case for all pathogenic prions. This scenario is consistent with the findings of Braak and coworkers, who have mapped the spread of aggregated α-synuclein called Lewy neurites from the gut into the brainstem and throughout the cerebral hemispheres (11, 13, 139).

Inherited Parkinson's Disease

Genetic linkage of the A53T mutation in the α-synuclein gene (140) led to the identification of α-synuclein in Lewy bodies that are found in both inherited and sporadic forms of PD (173). Duplication and triplication of the α-synuclein gene have also been reported in PD patients (66). Additionally, the G2019S variant in the leucine-rich repeat kinase 2 (LRRK2) protein imposes an increased risk for sporadic late-onset PD (71). Although mutations in other proteins have been identified as the causes of other forms of inherited PD, the relevance, if any, of these polypeptides to sporadic PD is unclear.

Tg mice expressing mutant human α-synuclein(A53T) were found to exhibit neurological disease at ~400 days of age (47). When brains from these ill mice were homogenized and injected into weanlings, the recipient mice became ill at ~200 days of age (110, 128). Recombinant α-synuclein was purified and induced to form fibrillar aggregates in vitro. After the introduction of aggregated α-synuclein into cultured cells, in Tg mice expressing mutant human α-synuclein(A53T), and in non-Tg mice, the aggregates of α-synuclein underwent self-propagation and, as such, became prions (109, 110, 117, 191).

Inherited Amyotrophic Lateral Sclerosis and SOD1 Prions

Studies of the progressive spread of motor neuron lesions along the neuraxis suggest an orderly and active process in ALS, also known as Lou Gehrig's disease (155). More than 150 different mutations in the gene encoding human SOD1 have been found to cause familial forms of ALS (189). Aggregates of mutant human SOD1(H46R) protein have been used to initiate self-propagation in cultured cells, which can continue indefinitely; as such, mutant SOD1(H46R) forms prions (129). In another study, two human SOD1 constructs harboring either the G127X or G85R mutation induced wild-type SOD1 to misfold and aggregate in human neural cell lines (58).

In addition to mutant SOD1, mutations in two RNA-binding proteins, TDP-43 and FUS, have been identified in patients with familial ALS. As well as being involved in RNA metabolism, TDP-43 and FUS form aggregates in neurons in some cases of ALS and FTD (139, 188). Recent evidence indicates that both TDP-43 and FUS contain fungal prion–like domains rich in glutamine and asparagine residues, and in the case of TDP-43, this domain contains a substantial number of disease-causing mutations.

Huntingtin Prions

Unlike the aforementioned NDs, HD is always inherited. The wild-type huntingtin protein harbors an N-terminal region of ~35 glutamine residues. An additional 5 to 20 glutamines, resulting from mutations in the huntingtin gene, are found in most patients with HD, but many more have also been recorded (101). The length of the polyglutamine expansion is inversely proportional to the age of onset of HD.

Expanded polyglutamine repeats in a fragment of the huntingtin protein show spontaneous aggregation that self-propagates in cultured cells; in other words, they may prove to be prions (156). The idea of huntingtin prions is attractive because it would explain why people with 5 to 10 additional glutamines do not become ill until they are 40 to 50 years of age even though the mutant protein is produced beginning in embryogenesis.

NONPATHOGENIC MAMMALIAN PRIONS

Importantly, some prions, such as CPEB and MAVS, in mammals are not known to cause disease but perform important cellular functions (76, 169, 170). Both CPEB and MAVS contain glutamine-rich domainssimilar to those found in most yeast prions. The CPEB prion seems to control localized gene transcription in long-term memory, and the MAVS prion features in the immune response to infection by some RNA viruses. Unexpectedly, the biologically active forms of CPEB and MAVS are the oligomeric prion states and not the

monomeric precursor proteins. Another nonpathogenic prion may be TIA-1, which is an RNA-binding protein that promotes translational arrest and the assembly of stress granules under conditions of cellular stress, including acute energy starvation (51). TIA-1 contains a carboxyterminal, glutamine-rich, prion-related domain that can undergo aggregation and thus functions as a metabolic switch. When this glutamine-rich domain of TIA-1 aggregates, stress granule formation ceases, but the process appears to be reversible.

FUNGAL PRIONS

Yeast prions have been invaluable in defining the spectrum of prions (20, 65, 197). The most extensively studied yeast prion is [PSI^+], in which the Sup35 protein becomes a prion and its polypeptide chain termination function is diminished. In other words, stop codons are ignored, and proteins are abnormally synthesized with carboxyterminal extensions. The prion domain of Sup35, which is rich in Gln and Asn residues, is located near the amino terminus. Studies of the prion domains of two [PSI^+] strains demonstrated that the more stable and more slowly replicating strain showed an extended, tightly packed β-sheet structure (184). The HET-s prion of *Podospora anserina*, which is a filamentous fungus, controls a programmed cell death reaction termed heterokaryon incompatibility (60). Although yeast prions are not infectious in the sense of being released into the culture medium and infecting other yeast, they are transmissible from mother to daughter cells and thus can readily multiply. Many of the lessons learned from studies of fungal prions are applicable to the NDs, such as AD, PD, and FTDs, in which prion infectivity is not readily demonstrable. As with fungi, special conditions, including cultured cells and generally Tg mice, must be used to demonstrate the existence and propagation of prions.

AMYLOIDS

The term amyloid was initially used to describe waxy substances that accumulate in tissues in a variety of systemic and CNS human disorders. The tinctorial properties of amyloid accumulation in tissues resembled those of some long-chain polysaccharides from plants referred to as starch. Features common to all amyloid fibrils are their nonbranched ultrastructure, their birefringence in polarized light after staining with Congo red dye, their shift in the fluorescence emission wavelength after staining with thioflavin T dye, and their crossed β-pleated sheet structure (31, 36, 52, 159, 185). Some of the most well-studied amyloids include the abnormal immunoglobulins, or paraproteins, that are produced by neoplastic plasma cells in multiple myeloma. Some of these aberrant immunoglobins,such as the Bence-Jones light chains, readily polymerize into amyloid fibrils. The accumulation of Bence-Jones paraproteins in the kidney leads to renal failure. Another protein, such as mutant transthyretin (TTR), shows diminished stability as a native tetramer and readily polymerizes into amyloid fibrils. TTR is a plasma protein that carries thyroxine and retinol-binding protein; it is also found in cerebrospinal fluid. The deposition of TTR amyloid fibrils within myelin sheaths and cardiac muscle causes polyneuropathy and cardiomyopathy, respectively. Recently, the drug Tafamidis [2-(3,5-dichloro-phenyl)-benzoxazole-6-carboxylic acid] was developed to stabilize the tetrameric structure of mutant TTR and is now being used to treat familial amyloidotic polyneuropathy (86).

In CNS disorders, amyloid plaques are a prominent feature in such diseases as kuru and AD (2, 31, 94). Subsequently, the proteins that polymerize into the fibrils of kuru and AD were identified as PrP^{Sc} and Aβ, respectively (9, 54). Unlike the Bence-Jones immunoglobulin light chains, both PrP^{Sc} and Aβ are prions in that each can acquire a conformation that becomes self-propagating. Although amyloid plaques are an essential feature of AD, they are nonobligatory features of kuru, CJD, scrapie, and other PrP^{Sc} disorders (151). Notably, a mouse scrapie prion strain was isolated that consistently produced PrP amyloid plaques (16). As with many mammalian prions, most yeast prions have a high β-sheet content and can polymerize into amyloid fibrils (93).

It is important to distinguish between prions and amyloids (138, 199); as noted above, prions need not polymerize into amyloid fibrils and can undergo self-propagation as oligomers (1, 5, 120, 171). The self-propagation of an alternative conformational state is a key feature of all prions. In contrast, amyloids are linear polymers that increase in number as new seeds are generated. It can be argued that any prion oligomer has the potential to become an amyloid seed; I contend that the polymerization of prions into amyloid fibrils represents a sequestration process whereby the brain seeks to minimize neurotoxicity. Although some investigators argue that any protein can be induced to polymerize into an amyloid fibril (33), only a small subset of proteins seems to become prions. Amyloid fibrils are not only pathogenic but they may also act as storage depots for secreted proteins (113).

CONCLUSIONS

The convergence of studies on these common neurodegenerative maladies has been remarkable (Table 1). Although many mysteries are now explicable within the framework of the prion concept, the science of prions is still in its infancy. Many unanticipated discoveries seem likely to emerge from the future study of prions.

Evidence that Prions Cause Many Different Neurodegenerative Disorders

Over the past few years, there has been a persuasive accumulation of new experimental data arguing that AD, PD, and the tauopathies are caused by prions. This advance in our understanding of the pathogenesis of these maladies will undoubtedly lead to new diagnostics and therapeutics. Notably, studies of NDs represent a curious mixture of outstanding advances and disappointing failures. Discovery of the Aβ peptide in cerebrovascular amyloid and plaques as well as the tau protein in tangles remains central to our understanding of AD pathogenesis. However, the current lack of any therapy that halts or even slows one ND is a colossal tragedy.

Studies of PrP prions are likely to be helpful in developing improved models and bioassays for Aβ, tau, and α-synuclein prions. The use of bigenic mice expressing mutant human APP and luciferase under control of the *Gfap* promoter (178, 194) is based on earlier studies of bigenic mice expressing luciferase and many different PrP transgenes (179, 195). The strategy for using mutant transgenes overexpressed in cells and mice involves increasing the likelihood that a particular protein will adopt a β-sheet-rich conformation that becomes self-propagating. In bigenic mice expressing mutant APP, the use of bioluminescence is proving

to be an invaluable adjunct because such mice do not develop overt clinical signs of neurological dysfunction.

Although no cultured cell systems for propagating Aβ prions have been developed, some excellent systems for propagating tau and α-synuclein prions are now available. Tau prions have been formed using tau fragments and the full-length protein in vitro by exposure to arachidonic acid. They are then introduced into cells where they recruit wild-type and/or mutant tau to become prions. Similar experimental protocols have been adopted for studies of α-synuclein prions.

Many aspects of NDs can be explained by prions. The relentless and continuous spread of prions in the CNS provides a plausible explanation for the uninterrupted progression of the NDs. Prions also provide a unifying mechanism by which late-onset neurodegeneration can be understood. Although germ line mutations are present from the beginning of embryogenesis in familial cases of AD, PD, and the tauopathies, a second event is needed to explain the late onset of these disorders. That event seems likely to be the generation of enough prions to create self-sustaining replication.

Among the NDs, the tauopathies offer a remarkably wide spectrum of illnesses with respect to clinical presentations as well as progression. These diseases include PSP, Pick's, CBD, FTLD, and AGD. Using fMRI to map connectivity networks, the progression of these different tauopathies can be defined in vivo. The most plausible explanations for these clinically distinct tauopathies seem to be different strains of tau prions with distinct neurotropisms.

Some Arguments Against Prions Causing Many Neurodegenerative Diseases

In contrast to CJD and kuru, there are no examples of person-to-person transmissions for AD, PD, and the tauopathies; on the basis of the lack of transmission, some investigators argue that prions do not cause these disorders (85). They also cite the inability of extracts from the brains of patients to transmit these disorders to wild-type animals as additional evidence against a prion etiology. Notably, α-synuclein prions have been transmitted to wild-type mice (108, 117). Choosing narrow criteria for defining prion diseases seems rather artificial and unhelpful in advancing our knowledge of the NDs. Moreover, this constricted definition ignores much of the information accumulated about prions over the past three decades. Although some prions replicate more rapidly and accumulate outside of cells, others do not. Fungal prions are not secreted into the media bathing yeast cells; rather, they remain intracellular and pass from mother to daughter cells as the yeast multiply (20, 198). Passage of yeast prions from an infected cell to an uninfected cell requires cytoduction, in which cytoplasmic mixing of the two fungal cells occurs. As such, fungal prions may be a better model for understanding the properties of prions causing many of the NDs.

It is not surprising that cultured cells and Tg mice that overexpress mutant transgenes are needed to demonstrate the transmission of some prions causing NDs. Elevated transgene expression generally shortens the incubation times in Tg mice infected with prions but there occasional exceptions (49, 151, 180). Human point mutations in the transgenes appear to facilitate transmission of Aβ, tau, and α-synuclein prions, not unlike the incidence of the

NDs. As noted above, the penetrance of familial forms of the NDs approaches 100%, whereas the prevalence of the sporadic forms of these disorders vary from one per million for CJD to 1 per 100 people for AD in the United States. Using transgene-encoded mutant proteins demands that the inoculated mice develop detectable neurodegeneration well before spontaneous disease in uninoculated controls is evident.

Implications of Prion Etiologies for Patient Care

The discovery that prions are not confined to a small group of disorders in which PrP^{Sc} prions accumulate has important implications for the development of informative molecular diagnostics and effective therapeutics. Early diagnosis will likely require molecular reporters, such as PET ligands, to identify prions long before symptoms appear. Such PET ligands would need to distinguish the normal protein precursors from the prion forms whether the proteins are PrP, Aβ, tau, or α-synuclein. Although there is considerable interest in using the levels of Aβ and tau in cerebrospinal fluid for the diagnosis of AD, changes in the levels of these proteins are generally small and may prove problematic in monitoring responses to therapeutic interventions. Additionally, meaningful treatments are likely to require cocktails of drugs that diminish the precursor protein, interfere with the conversion of precursors into prions, and/or enhance the clearance of prions.

Some investigators have expressed concern that the transmissibility of prions will result in patients with AD receiving less attention than they need, particularly those who are incontinent and those who have trouble handling their own saliva (67). Although a recent study argues that there is no evidence for the person-to-person transmission of Aβ, tau, or α-synuclein prions (85), it may prove wise to institute some minimal precautions in care of AD and PD patients that resemble in some ways those followed in the care of patients with CJD and HIV until definitive investigations can be performed. The history of CJD and AIDS is full of regrets where earlier vigilance might have prevented many deaths. It would be a mistake to deny a prion etiology for these common illnesses under the guise of facilitating the care of patients.

Equally important is the issue of prion contamination of biologics prepared from patients with AD, PD, and the tauopathies. The contamination of cadaveric human growth hormone preparations with CJD prions is a sad chapter in the development of therapeutics for children with short stature (124). Four people with variant (v) CJD, contracted from eating tainted beef prepared from “mad” cows, unknowingly transmitted vCJD prions to recipients of blood transfusions (70, 72, 137). Dura mater grafts and cornea transplants have also transmitted CJD prions (166). Inadequately sterilized surgical instruments and implanted electrodes have transmitted sporadic (s) CJD prions (7). PrP^{Sc} prions have been shown to bind tightly to stainless steel wires and retain infectivity (50, 204). Aβ prions also bind to steel wires and induce Aβ deposition in the brains of Tg mice (34).

The risk of transmitting Aβ, tau, α-synuclein, or even SOD1 prions through biologics, organ grafts, or inadequately sterilized surgical instruments has not been well studied because the transmissibility of these proteins has only been recently appreciated and the bioassays are not well developed (74). Endpoint titrations, incubation times, and bioluminescence imaging have been used to measure PrP prion titers in fractions prepared from prion-infected

mammals (37, 82, 147, 179). Overexpression of wild-type PrP transgenes has generally been found to decrease the incubation times as measured from inoculation to a sustained increase in the BLI signals or to the onset of progressive neurological dysfunction (15, 151, 180, 195), although there are exceptions (49). Purified recombinant tau and α-synuclein have been induced to aggregate in vitro and used to initiate prion replication in cultured cells, but such systems have not yet been used to measure prion titers. Although Tg mice have been used to detect the presence of Aβ, tau, and α-synuclein prions in mouse and human brains, quantitative assays need to be developed. Creating such measurement methods is important in assessing the risk of biologics and organ transplants prepared from patients with neurodegeneration as well as in determining the number of such prions that may contaminate surgical instruments and prosthetics, including chronically implanted electrodes. Of particular concern may be the increasing number of patients with PD, who are having neurosurgical procedures for implantation of deep brain stimulation electrodes (132). It remains uncertain whether more stringent guidelines for such procedures need to be established.

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Acronyms

AD	Alzheimer’s disease
ALS	amyotrophic lateral sclerosis
APP	amyloid precursor protein
CJD	Creutzfeldt-Jakob disease
CTE	chronic traumatic encephalopathy
CWD	chronic wasting disease
FTD	frontotemporal dementia
FTLD	frontotemporal lobar degeneration
GSS	Gerstmann–Sträussler–Scheinker disease
HD	Huntington’s disease
ND	neurodegenerative disease
NFT	neurofibrillary tangle
PD	Parkinson’s disease
Prions	proteins that acquire alternative conformations that become self-propagating

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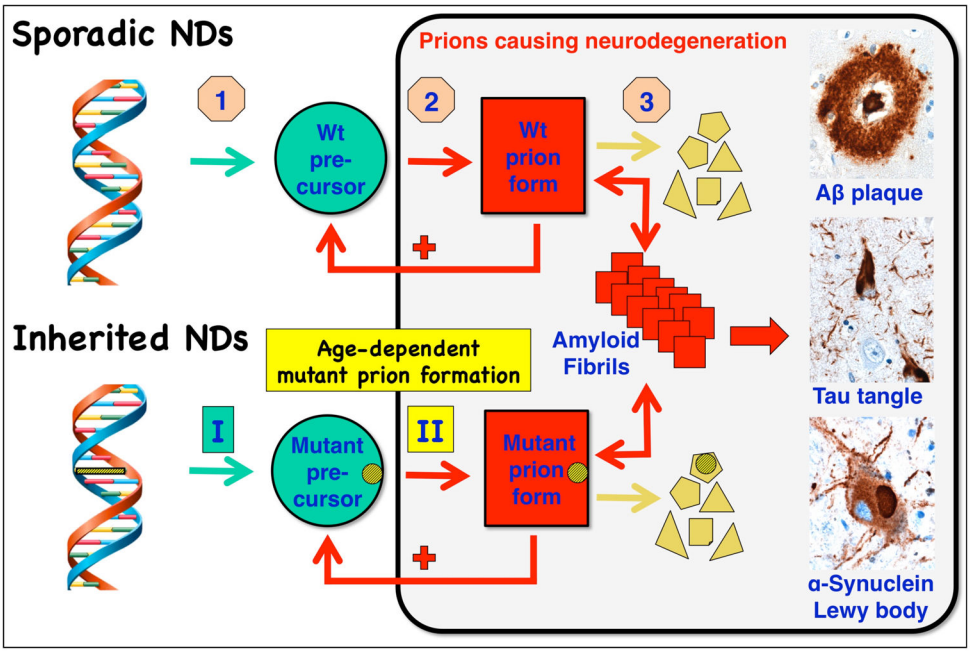

Figure 1.

Neurodegeneration caused by prions. (Sporadic NDs) In sporadic neurodegenerative diseases (NDs), wild-type (wt) prions multiply through self-propagating cycles of posttranslational modification during which the precursor protein (green circle) is converted into the prion form (red square), which generally is high in β-sheet content. Pathogenic prions are most toxic as oligomers and less toxic after polymerization into amyloid fibrils. The small polygons (pale yellow) represent proteolytic cleavage products of the prion. Depending on the protein, the fibrils coalesce into Aβ amyloid plaques in Alzheimer's disease (AD), neurofibrillary tangles in AD and Pick's disease, or Lewy bodies in Parkinson's disease and Lewy body dementia. Drug targets for the development of therapeutics (beige octagons): (1) lowering the precursor protein, (2) inhibiting prion formation, and (3) enhancing prion clearance. (Inherited NDs) Late-onset heritable neurodegeneration argues for two discrete events: the first event (green rectangle I) is the synthesis of mutant precursor protein (green circle) and the second event (yellow rectangle II) is the age-dependent formation of mutant prions (red square). The yellow bar with diagonal lines in the DNA structure represents mutation of a base pair within an exon, and the small yellow circles with diagonal lines signify the corresponding mutant amino acid substitution.

Table 1

Neurodegenerative diseases caused by prions.

Neurodegenerative diseases	Causative prion proteins	Percent inherited
Creutzfeldt-Jakob disease	PrP^{Sc}	10–20
Gerstmann-Sträussler-Scheinker		90
Fatal insomnia		90
Bovine spongiform encephalopathy		0
Scrapie		0
Chronic wasting disease		0
Alzheimer's disease	Aβ → tau	10–20
Parkinson's disease	α-synuclein	10–20
Frontotemporal dementia (FTD) Posttraumatic FTD, called chronic traumatic encephalopathy	tau, TDP43, FUS, C9orf72 (progranulin)	10–20
Amyotrophic lateral sclerosis	SOD1, TDP43, FUS, C9orf72	10–20
Huntington's disease	huntingtin	100

Table 2

Some possible explanations for late-onset neurodegeneration

1. Mitochondrial DNA mutations (26, 125)
2. Oxidative modifications of DNA, lipids, or proteins (87, 100)
3. Impaired autophagy (133)
4. Altered apoptosis (201)
5. Posttranslational chemical modification (201)
6. Modified innate immunity (186)
7. Accumulation of exogenous toxins, such as heavy metals, alcohol, drugs, and hormones (19)
8. Concomitant conditions, such as atherosclerosis (96)
9. RNA-DNA differences (107)
10. Chaperone malfunction (111)
11. Somatic mutations (100)
12. Altered regulation of transcription (8)
13. Haploinsufficiency (30, 153)
14. Postinfectious syndromes of the central nervous system, including late polio, subacute sclerosing leukoencephalitis, postencephalitic Parkinson's disease, and Lyme disease (59, 89, 203)
15. Modifier genes, such as apolipoprotein E and LRRK2 (17, 25)
16. Polyglutamine expansions (101, 196)
17. Dipeptide repeat proteins (127)
18. Cu^{2+} binding to expanded PrP octarepeat region (177)
19. Prion formation and accumulation (134, 144)

Table 3

Genetic correlates of the neuropathological subtypes of frontotemporal lobar degeneration (FTLD)[a]

Molecular classification	Neuropathological subtype[b]	Mutated genes[b]
FTLD-tau	Pick's disease	*MAPT*
	Corticobasal degeneration	*MAPT*
	Progressive supranuclear palsy	*MAPT*
	Argyrophilic grain disease	*MAPT*
	Neurofibrillary tangle–predominant dementia	*MAPT*
	Multiple system tauopathy with dementia	*MAPT*
	White matter tauopathy with globular glial inclusions	*MAPT*
FTLD–TAR DNA-binding protein 43	Type A	*GRN*
		C9orf72
	Type B	*C9orf72*
	Type C	
	Type D	*VCP*
FTLD–fused in sarcoma	Atypical FTLD with ubiquitinated inclusions	*FUS*
	Neuronal intermediate filament inclusion disease	*FUS*
	Basophilic inclusion body disease	*FUS*
FTLD–ubiquitin proteasome system	Frontotemporal dementia linked to chromosome 3	*CHMP2B*

[a] Adapted from Reference 154.

[b] Characteristic pattern of pathology, not the clinical syndrome.