Prion-like mechanisms in neurodegenerative diseases

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Abstract | Many non-infectious neurodegenerative diseases are associated with the accumulation of fibrillar proteins. These diseases all exhibit features that are reminiscent of those of prionopathies, including phenotypic diversity and the propagation of pathology. Furthermore, emerging studies of amyloid-β, α-synuclein and tau — proteins implicated in common neurodegenerative diseases — suggest that they share key biophysical and biochemical characteristics with prions. Propagation of protein misfolding in these diseases may therefore occur through mechanisms similar to those that underlie prion pathogenesis. If this hypothesis is verified *in vivo*, it will suggest new therapeutic strategies to block propagation of protein misfolding throughout the brain.

Prionopathies are unique among neurodegenerative diseases because they are infectious — that is, spontaneous transmission from one individual to another has occurred outside an experimental setting. Prion diseases result from protein misfolding, which in rare cases can be due to exposure to exogenous prion species[1] — that is, infection — but is usually due to events that occur spontaneously in the individual. The non-pathogenic form of the prion protein (PrP^{C}) is expressed in many human cell types[2]. When PrP^{C} comes into contact with a pathogenic prion protein conformer (PrP^{Sc}), it is induced to misfold in a process known as templated conformation change. Through this interaction, the conformation of a PrP^{Sc} molecule is communicated to a native PrP^{C} protein[3]. This interaction may involve other proteins in the cell, and it is unknown whether one or more PrP^{Sc} molecules is required to form the pathogenic 'seed'.

Recent studies have highlighted prion-like mechanisms of propagation of protein misfolding in various common, non-infectious neurodegenerative diseases (those in which transmission between individuals has never been shown outside experimental conditions), such as Alzheimer's disease (AD), frontotemporal dementia (FTD), Parkinson's disease (PD) and polyglutamine diseases (TABLE 1). Like prionopathies, all of these diseases are associated with the accumulation of fibrillar aggregates of proteins —tau, amyloid-β (Aβ), α-synuclein and polyglutamine proteins. With the exception of polyglutamine diseases, which arise from an unusual genetic mutation that produces a protein containing an abnormally long glutamine tract, sporadic cases of these diseases involve the wild-type form of each gene, whereas rarer, autosomal dominant forms of the diseases are linked to missense or splicing mutations. Similarly, although prion diseases are defined by their infectivity, most prion disease cases actually arise sporadically from wild-type protein or through inherited mutations in the prion protein[4].

This article highlights two important commonalities between prion and non-prion neurodegenerative diseases — phenotypic diversity and spreading pathology — and reviews the basic research that is beginning to elucidate the biochemical and cellular basis of these similarities.

Phenotypic diversity

Most common neurodegenerative diseases manifest myriad phenotypes. In AD, the speed of cognitive decline, age of onset and the location and extent of Aβ plaque load vary considerably[5–7]. Aβ aggregates are also present in muscle fibres in inclusion body myositis, a common age-related inflammatory muscle disease[8], and in the vascular wall in cerebral amyloid angiopathy[9]. PD, dementia with Lewy bodies and multiple system atrophy are all associated with α-synuclein deposition[10] but are strikingly distinct clinical syndromes. PD is associated with α-synuclein missense mutations[11,12] and gene amplification[13–15]. Most remarkably, tau aggregation is a pathological hallmark of more than 20 different neurodegenerative diseases, including AD[10] and frontotemporal dementia with Parkinsonism, a familial disease caused by mutations in the tau gene[10]. Sporadic tauopathies vary considerably in brain region involvement, disease duration, age of onset and fibril morphology[10].

Prion diseases also have diverse phenotypes, involving both the CNS and PNS, exhibit distinct rates of progression[16,17] and can derive from mutations in the prion protein gene[18]. The wild-type prion protein (PrP) is the causative agent for Kuru[19] and sporadic Creutzfeldt-Jakob Disease (CJD), among others. Prions also cause fatal familial insomnia[20–22]. Thus, variation in the presentation and course of the disease defines both prion- and non-prion-based neurodegeneration. Distinct conformations of pathogenic proteins could have a key role in determining the phenotypic diversity of non-infectious neurodegenerative diseases.

Underlying mechanisms: conformations and strains? In the case of the prion diseases, it is thought that distinct conformers, or strains, of prion fibril underlie different disease phenotypes. Depending on various factors, including amino acid sequence, post-translational modifications and aggregation conditions, PrP^{Sc} assembles into multiple individually self-propagating conformations that generate these distinct disease phenotypes in humans and mice[22–24]. It is not yet possible to predict the specific phenotype that will result from a given PrP^{Sc} conformation in mammals. However, the yeast prion Sup35 has helped inform our understanding of mammalian prions. Sup35 alternates between a soluble (active) and aggregated

(inactive) state. The aggregation state of Sup35 is transmitted in a heritable, epigenetic fashion from parent to daughter yeast cell. The rate of growth and fibril fragility determine the efficiency with which protein aggregates are passed from mother to daughter cells[25], and these biochemical features have been directly linked to fibril structure[26]. This level of structural detail is not yet available for PrP^{Sc}; however, recent work in mouse models indicates that unique prion strains correlate with the sensitivity of the associated fibrils to *in vitro* denaturation[24].

To what extent can conformational diversity explain the diverse phenotypes of the non-infectious neurodegenerative diseases? The conformational diversity of various amyloid proteins is now widely recognized. For example, tau fibrils can exist in several distinct structures that are stable over serial seeding reactions[27]. Wild-type, ΔK280 and P301L;V337M double-mutant fibrils are conformationally distinct when prepared *in vitro*. When mutant tau seeds are used to induce fibrillization of wild-type monomer, the resulting fibrils closely resemble the conformation of the mutant seed and are distinct from the wild-type fibril conformation[27].

Distinct, self-propagating fibril structures have also been documented for Aβ[28] and α-synuclein[29], putting these proteins in the same biochemical class as prions. Even the growth conditions of *in vitro* Aβ fibrillization reactions have been shown to specify the conformation of the resultant fibrils[28]. Aβ fibrils assume one of two distinct conformations, depending on whether the reactions are gently agitated. When incubated with fresh Aβ monomer, each fibril type faithfully propagates the original conformation over successive seeding reactions. The two Aβ fibril conformations have distinct toxicities when added to primary neurons[28]. Although intriguing, this artificial readout of fibril toxicity is of unknown significance in relation to the diversity of human disease, and thus at this stage one can only speculate as to the effect of distinct Aβ conformers on AD phenotypes *in vivo*.

α-Synuclein proteins also exhibit fibrillar conformational diversity, as missense mutations that are responsible for dominantly inherited synucleinopathy produce fibrils that are conformationally distinct from wild-type fibrils[29,30]. *In vitro* studies indicate that mutant fibrils can transmit their conformation to wild-type protein, driving it into a new conformation that resembles the original mutant seed[29]. Again, however, there is as yet no evidence that distinct synuclein structures underlie the various synucleinopathy phenotypes.

Taken together, these *in vitro* studies indicate that tau, Aβ and α-synuclein are all capable of the type of templated conformation change that was first described for prions. Like prions, these proteins also form distinct conformers *in vivo* that could cause variation in regional pathology and disease progression. Extrapolating from fundamental research in prion biology, which indicates that factors such as chaperones can modify prion amplification rates, formation of these distinct conformers could be influenced by specific protein interactions or post-translational modifications. These extragenic effects might manifest as genetic modifiers of pathogenesis, just as the presenilins increase AD risk by augmenting production of Aβ. Additionally, aggregates could produce unique patterns of disease through conformation-specific interactions with other cellular factors, which likewise might appear as genetic modifiers. The relative ease with which it is possible to generate distinct protein fibril conformers *in vitro* indicates that there might be even more pathological syndromes than those of which we are currently aware. However, until distinct mammalian pathologies are clearly linked to discrete protein conformations, or genetic modifiers in humans are directly associated with the production of unique fibril conformations, it will be unclear whether prion-like conformational diversity of pathological proteins accounts for phenotypic variation in the common neurodegenerative diseases.

Spreading pathology

Neurodegenerative diseases begin with dysfunction in a discrete region, whereas at later stages they typically involve much larger areas of the brain. Pathology often occurs in particular neural networks and progresses in a predictable manner. For example, the *trans*-entorhinal region is the first area to show signs of deterioration and tau pathology in AD. Glutamatergic cells in this region project into the entorhinal cortex, which is the next area to degenerate. Lesions of the hippocampus, amygdala and neocortex follow[31]. Recent studies of patients with and without dementia using functional imaging have corroborated these pathological studies and have shown that degeneration in distinct neurodegenerative diseases such as AD, corticobasal ganglionic degeneration and FTD follow normal patterns of intrinsic neuronal connectivity[32]. PD is well known to begin with motor symptoms that are largely caused by the degeneration of dopaminergic neurons in the substantia nigra; however, a substantial fraction of patients go on to develop dementia, implying that additional brain regions are involved[33]. Likewise, in amyotrophic

Table 1 | **Common features of mammalian proteins associated with neurodegenerative diseases**

Protein	Conformational diversity?	*Trans*-cellular aggregate movement in culture?	Aggregate propagation *in vivo*?
Prion protein (PrP)	Yes[21,22]	Yes[39–41]	Yes[4]
Amyloid-β	Yes[28]	Extracellular aggregates are taken up by cells[39]	Yes: inoculation of brain triggers further aggregation[52]
Tau	Yes[27]	Extracellular aggregates are taken up by cells and transfer of intracellular aggregates occurs[49]	Yes: extracellular inoculation with aggregates triggers uptake of aggregates and induces further intracellular tau misfolding[53]
α-Synuclein	Yes[29]	Protein is released by cells and taken up by co-cultured cells[46]	Possibly: in humans, transplanted cells develop Lewy bodies[43–45]; transplanted cells in mice take up protein from host and form inclusions[46]
Polyglutamine	Yes[60]	Aggregates are taken up by cultured cells and trigger misfolding of wild-type protein; aggregates can move between cells[50]	Not demonstrated

lateral sclerosis, the progression of symptoms locally in the spinal cord and the combined degeneration of upper and lower motor neurons is well known[34]. Taken together, these observations suggest a pathogenic link between one affected cell and its neighbour. However, there is not yet clear experimental evidence that this progression of non-prion neurodegenerative diseases results from the 'spread' of disease from one area to another.

Prionopathies begin with a tiny inoculum, such as a contaminated surgical device or transplanted tissue, or the spontaneous accumulation of PrP^{Sc} in a single cell or group of cells. Ultimately, however, pathology involves a large area of the nervous system[35]. Evidence suggests that PrP^{Sc} propagates through neuronal networks. In hamsters, orally derived PrP^{Sc} seems to spread along the vagus nerve to the medulla, pons, midbrain, cerebellum and thalamus via neuroanatomical pathways[36]. Furthermore, two studies have observed that PrP^{Sc} injected into the eye travels along defined neuroanatomical connections to reach larger brain regions[37,38].

Underlying mechanisms: cell-to-cell transmission? The propagation of PrP misfolding between cells follows a model in which PrP^{Sc} travels from an infected cell to a naive cell, whereupon it encounters PrP^{C} and converts it to PrP^{Sc} (REF. 38). These features of prion disease suggest that PrP^{Sc} may gain access to a connected neuron by traversing the synapse, or that PrP^{Sc} released into the extracellular space may be taken up by nearby cells. Cell culture studies support these hypotheses. Cultured primary mouse neurons spontaneously take up fibrillar PrP, which localizes to late endosomes and/or lysosomes[39]. PrP aggregates may transfer between cultured cells through exosomes[40] or tunneling nanotubes[41], which are putative cytoplasmic connections between mammalian cells[42]. Determining whether these events underlie the spread of prion pathology *in vivo* will require more mechanistic studies involving targeted disruption of these processes.

It is unknown whether non-prion protein aggregates move between cells in humans. Pathological studies of patients with PD who underwent fetal transplant surgery are provocative but not conclusive. In these reports, engrafted mesencephalic dopaminergic neurons developed ubiquitin- and α-synuclein-positive Lewy bodies, many of which were indistinguishable from lesions in the diseased host[43–45]. Recent studies in mice have essentially replicated the work in patients: synuclein-negative cells were transplanted into a human synuclein-transgenic mouse, where they developed Lewy bodies[46]. This investigation clearly indicates that synuclein is capable of *trans*-cellular movement *in vivo*, and has obvious implications for the potential of aggregated protein to spread pathology from cell to cell in humans.

Whether aggregates can transfer directly between cells *in vivo* is unknown, but cell culture studies suggest this is possible. For example, aggregates comprised of Aβ, α-synuclein, tau and polyglutamine proteins are readily internalized by cultured cells[39,46–50]. In the case of polyglutamine proteins, the uptake of an aggregate causes the wild-type (unexpanded) form of the protein expressed in the cell to misfold[50]. Similarly, internalized tau aggregates seem to interact directly with normally folded tau and trigger its fibrillization[49]. Intracellular tau aggregates can also transfer between co-cultured cells[49]. Thus, tau and polyglutamine proteins, like prions, can 'transmit' a misfolded state from the outside of a cell to the inside. This idea is supported by the observation that the yeast prion, Sup35, can accomplish *trans*-cellular propagation of aggregates when expressed in mammalian cells[51]. Although the results of these experiments are intriguing, a clearer interpretation will require the definition of basic mechanisms of uptake and cell–cell transfer, as well as the demonstration that this influences propagation of pathology *in vivo*.

Intracerebral injection of human or mouse AD brain material can initiate Aβ pathology in transgenic mice[52]. It has also been observed recently that microinjections of brain extracts from transgenic mice expressing mutant human tau protein induce misfolding of endogenous tau in recipient mice. It was suggested that the induced tau misfolding propagated beyond the site of injection. Indeed, tau protein must be present in the injected material for this effect to manifest, which hints at a 'prion-like' mechanism[53], although it is hard to rule out diffusion of the injected material accounting for the apparent propagation of endogenous tau misfolding. Although sporadic neurodegenerative diseases do not derive from injected brain extracts, these studies indicate that misfolding can somehow be communicated from the extracellular to the intracellular space, as was previously observed with tau in tissue culture[49]. It has not yet been demonstrated *in vivo* that a misfolded protein in one cell can directly trigger misfolding in a connected cell, which would more explicitly test the idea that AD, tauopathy or synucleinopathies involve prion-like mechanisms. In addition it should be emphasized that there is no evidence that these disorders have ever been transmitted between individuals as bona fide prionopathies.

Distinctions between diseases

Crucial distinctions remain between the prionopathies and common neurodegenerative diseases. Most importantly, there is no evidence, despite decades of study, of true, spontaneous infectivity for any sporadic disease such as AD, FTD or PD. The biophysical properties that allow a protein that has been eaten, passed through the digestive system and absorbed to replicate in the host and make its way to the brain clearly set prion proteins apart from any other known amyloid protein associated with neurodegenerative disease. However, serum amyloidosis A (SAA) has been studied as another potentially infectious amyloid disease[54]. It is caused by misfolding of the serum amyloid A protein[55] and although not associated with neurodegeneration has many features similar to prionopathies, including an oral route of transmission[56].

Most prionopathies exhibit relatively rapid progression in the CNS, with sCJD averaging 4–6 months from symptom onset to death[57], whereas common neurodegenerative diseases generally progress over many years. Furthermore, PrP is a transmembrane protein, which could in theory more easily allow *trans*-cellular propagation, whereas tau and synuclein normally function within the cell. Thus, it is more difficult to understand how they could accomplish *trans*-cellular movement.

A common model of propagation?

Even taking into account these distinctions, increasing experimental evidence is now indicating that the basic cellular mechanisms of *trans*-cellular prion propagation may be applicable to a wide range of protein pathologies. In this model (FIG. 1), fibrillar protein seeds from adjacent or synaptically connected cells may be taken up to induce the aggregation of otherwise normally structured protein. The propensity for this to occur could be influenced by splice isoforms and post-translational modifications of the proteins involved. This model could explain both the phenotypic diversity

observed in sporadic neurodegenerative disease, in which a single protein underlies various conditions, and the inexorable spread of pathology, in which aggregates can move between cells to propagate misfolding. It can also explain the involvement of neuronal networks in neurodegeneration. If these ideas are fully validated in animal models, they will suggest an important new conceptual framework with which to consider the pathogenesis of an enormous range of neurodegenerative diseases.

Implications for treatment

If non-infectious neurodegenerative diseases and prionopathies have similar mechanisms of progression, this will have important therapeutic implications. Current therapies for neurodegenerative diseases generally target nonspecific mechanisms to prevent cell death and promote neuron survival, or focus on disease-specific events that govern the stability and clearance of target proteins inside and outside cells. If protein misfolding in one cell can trigger similar events in a neighbour, then new therapeutic strategies based on halting non-cell-autonomous effects will be required. For example, stem cell therapies may have limited utility unless it is possible to render the transplanted cells resistant to the effects of misfolded protein from the host. Conversely, new approaches based on antibody therapies may have much wider application than previously realized, as so far the main focus as been on extracellular Aβ. Indeed, vaccination of mice in experimental models of tauopathy and synucleinopathy (which involve intracellular proteins) has been reported to ameliorate pathology[58,59]. Finally, as mechanisms of aggregate uptake and cell-to-cell transmission are determined, it may be possible to design new pharmacological interventions that block disease progression (FIG. 2).

Conclusions

Various neurodegenerative disease-associated proteins exhibit templated conformational change, which might underlie certain aspects of the phenotypic diversity of these diseases. Given the clear predictions of this model, future studies should be able to explicitly test this idea. The phenomenon of cell–cell transfer of protein aggregates is now well established in cell culture and mouse models in addition to those based on PrP pathogenesis will allow us to test whether other disease-related proteins can trigger a true propagation of misfolding in the manner of prions — that is, will aggregated species released from one cell and taken up by another lead to further aggregation of natively folded species in the recipient cell, and so on? The cellular mechanisms of aggregate release and uptake remain to be elucidated, and whether the same mechanisms apply to all aggregation-prone proteins will need to be determined. Similarly, the true range of these phenomena in other neurodegenerative diseases associated with protein misfolding is unknown. For example, will TAR DNA-binding protein 43 or superoxide dismutase 1, both of which are associated with amyotrophic lateral sclerosis, also exhibit such cell-to-cell transfer? It is also unknown what role glia and their proposed cellular mechanisms might have *in vivo*. Can aggregates transfer across synapses, and can this account for the propagation of pathology along neural networks? As the current studies and existing knowledge of prion pathogenesis are extended and augmented by new findings, a new unifying model that melds cell-autonomous and non-cell-autonomous mechanisms of protein misfolding in neurodegenerative diseases will be required.

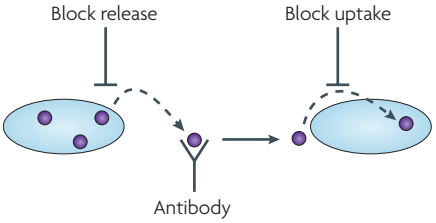

Figure 2 | **New therapeutic approaches.** If *trans*-cellular propagation of protein misfolding occurs, new strategies could supplement existing approaches to promote cell survival and block intracellular accumulation of misfolded species. As the cellular mechanisms of aggregate release and uptake are delineated, it may be possible to inhibit these events pharmacologically or genetically. Antibody-based therapies might also be expanded to target protein aggregates that are generated inside a cell and released into the extracellular space.

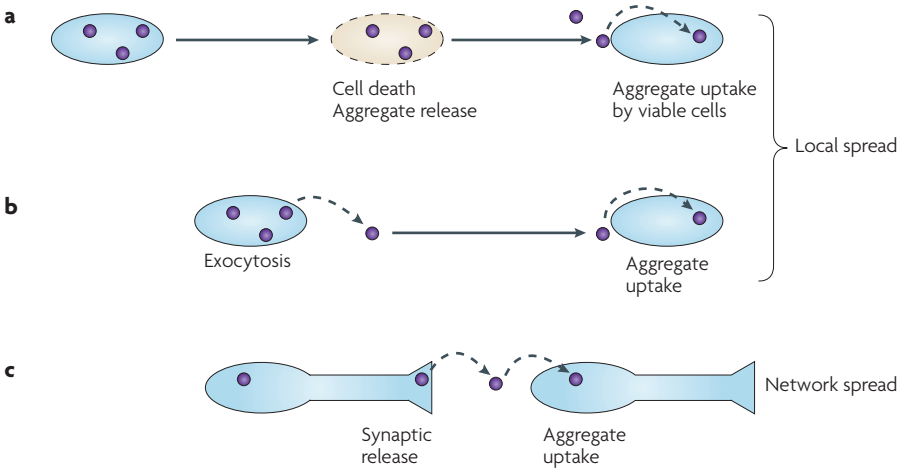

Figure 1 | **Potential mechanisms for *trans*-cellular propagation of protein misfolding.** **a** | Intracellular protein aggregation leads to cell death. This releases protein aggregates into the extracellular space, which are subsequently taken up by and corrupt protein folding in vulnerable cells. **b** | As part of the normal physiological processes of a living cell, protein aggregates may be released, potentially from exosomes or through exocytosis. This results in the presence of protein aggregates in the extracellular space that may be taken up by adjacent cells. Together with the mechanism shown in **a**, this process might account for local propagation of misfolding. **c** | Aggregates might cross synapses. Release could be due to local degeneration of a synapse, could be part of normal synaptic physiology or could be part of an exocytic process (as in **b**). This mechanism can explain network degeneration in neurodegenerative diseases.

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1. Prusiner, S. B. Novel proteinaceous infectious particles cause scrapie. *Science* **216**, 136–144 (1982).
2. Caughey, B., Race, R. E. & Chesebro, B. Detection of prion protein mRNA in normal and scrapie-infected tissues and cell lines. *J. Gen. Virol.* **69**, 711–716 (1988).
3. Pan, K. M. *et al.* Conversion of alpha-helices into beta-sheets features in the formation of the scrapie prion proteins. *Proc. Natl Acad. Sci. USA* **90**, 10962–10966 (1993).

4. Prusiner, S. B. Prions. *Proc. Natl Acad. Sci. USA* **95**, 13363–13383 (1998).
5. Williamson, J., Goldman, J. & Marder, K. S. Genetic aspects of Alzheimer disease. *Neurologist* **15**, 80–86 (2009).
6. Armstrong, R. A., Nochlin, D. & Bird, T. D. Neuropathological heterogeneity in Alzheimer's disease: a study of 80 cases using principal components analysis. *Neuropathology* **20**, 31–37 (2000).
7. Chui, H. C., Teng, E. L., Henderson, V. W. & Moy, A. C. Clinical subtypes of dementia of the Alzheimer type. *Neurology* **35**, 1544–1550 (1985).
8. Askanas, V. & Engel, W. K. Inclusion-body myositis: a myodegenerative conformational disorder associated with Aβ, protein misfolding, and proteasome inhibition. *Neurology* **66**, S39–S48 (2006).
9. Glenner, G. G. & Wong, C. W. Alzheimer's disease: initial report of the purification and characterization of a novel cerebrovascular amyloid protein. *Biochem. Biophys. Res. Commun.* **120**, 885–890 (1984).
10. Goedert, M. *et al.* From genetics to pathology: tau and alpha-synuclein assemblies in neurodegenerative diseases. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **356**, 213–227 (2001).
11. Polymeropoulos, M. H. *et al.* Mutation in the α-synuclein gene identified in families with Parkinson's disease. *Science* **276**, 2045–2047 (1997).
12. Zarranz, J. J. *et al.* The new mutation, E46K, of α-synuclein causes Parkinson and Lewy body dementia. *Ann. Neurol.* **55**, 164–173 (2004).
13. Ibanez, P. *et al.* Causal relation between α-synuclein gene duplication and familial Parkinson's disease. *Lancet* **364**, 1169–1171 (2004).
14. Singleton, A. B. *et al.* α-Synuclein locus triplication causes Parkinson's disease. *Science* **302**, 841 (2003).
15. Chartier-Harlin, M. C. *et al.* α-Synuclein locus duplication as a cause of familial Parkinson's disease. *Lancet* **364**, 1167–1169 (2004).
16. Ironside, J. W., Ritchie, D. L. & Head, M. W. Phenotypic variability in human prion diseases. *Neuropathol. Appl. Neurobiol.* **31**, 565–579 (2005).
17. Wadsworth, J. D. & Collinge, J. Update on human prion disease. *Biochim. Biophys. Acta* **1772**, 598–609 (2007).
18. Hsiao, K. *et al.* Linkage of a prion protein missense variant to Gerstmann-Straussler syndrome. *Nature* **338**, 342–345 (1989).
19. Gajdusek, D. C. Unconventional viruses and the origin and disappearance of kuru. *Science* **197**, 943–960 (1977).
20. Prusiner, S. B. Prion diseases and the BSE crisis. *Science* **278**, 245–251 (1997).
21. Bessen, R. A. *et al.* Non-genetic propagation of strain-specific properties of scrapie prion protein. *Nature* **375**, 698–700 (1995).
22. Telling, G. C. *et al.* Evidence for the conformation of the pathologic isoform of the prion protein enciphering and propagating prion diversity. *Science* **274**, 2079–2082 (1996).
23. Safar, J. *et al.* Eight prion strains have PrP^{Sc} molecules with different conformations. *Nature Med.* **4**, 1157–1165 (1998).
24. Legname, G. *et al.* Continuum of prion protein structures enciphers a multitude of prion isolate-specified phenotypes. *Proc. Natl Acad. Sci. USA* **103**, 19105–19110 (2006).
25. Tanaka, M., Collins, S. R., Toyama, B. H. & Weissman, J. S. The physical basis of how prion conformations determine strain phenotypes. *Nature* **442**, 585–589 (2006).
26. Toyama, B. H., Kelly, M. J., Gross, J. D. & Weissman, J. S. The structural basis of yeast prion strain variants. *Nature* **449**, 233–237 (2007).
27. Frost, B., Ollesch, J., Wille, H. & Diamond, M. I. Conformational diversity of wild-type Tau fibrils specified by templated conformation change. *J. Biol. Chem.* **284**, 3546–3551 (2009).
28. Petkova, A. T. *et al.* Self-propagating, molecular-level polymorphism in Alzheimer's β-amyloid fibrils. *Science* **307**, 262–265 (2005).
29. Yonetani, M. *et al.* Conversion of wild-type α-synuclein into mutant-type fibrils and its propagation in the presence of A30P mutant. *J. Biol. Chem.* **284**, 7940–7950 (2009).
30. von Bergen, M. *et al.* Assembly of tau protein into Alzheimer paired helical filaments depends on a local sequence motif (^{306}VQIVYK^{311}) forming β structure. *Proc. Natl Acad. Sci. USA* **97**, 5129–5134 (2000).
31. Braak, H. & Braak, E. Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathol. (Berl.)* **82**, 239–259 (1991).
32. Seeley, W. W., Crawford, R. K., Zhou, J., Miller, B. L. & Greicius, M. D. Neurodegenerative diseases target large-scale human brain networks. *Neuron* **62**, 42–52 (2009).
33. Hobson, P. & Meara, J. The detection of dementia and cognitive impairment in a community population of elderly people with Parkinson's disease by use of the CAMCOG neuropsychological test. *Age Ageing* **28**, 39–43 (1999).
34. Cudkowicz, M., Qureshi, M. & Shefner, J. Measures and markers in amyotrophic lateral sclerosis. *NeuroRx* **1**, 273–283 (2004).
35. Brown, P., Preece, M. A. & Will, R. G. "Friendly fire" in medicine: hormones, homografts, and Creutzfeldt-Jakob disease. *Lancet* **340**, 24–27 (1992).
36. Beekes, M., McBride, P. A. & Baldauf, E. Cerebral targeting indicates vagal spread of infection in hamsters fed with scrapie. *J. Gen. Virol.* **79**, 601–607 (1998).
37. Fraser, H. Neuronal spread of scrapie agent and targeting of lesions within the retino-tectal pathway. *Nature* **295**, 149–150 (1982).
38. Brandner, S. *et al.* Normal host prion protein (PrPC) is required for scrapie spread within the central nervous system. *Proc. Natl Acad. Sci. USA* **93**, 13148–13151 (1996).
39. Magalhaes, A. C. *et al.* Uptake and neuritic transport of scrapie prion protein coincident with infection of neuronal cells. *J. Neurosci.* **25**, 5207–5216 (2005).
40. Fevrier, B. *et al.* Cells release prions in association with exosomes. *Proc. Natl Acad. Sci. USA* **101**, 9683–9688 (2004).
41. Gousset, K. *et al.* Prions hijack tunnelling nanotubes for intercellular spread. *Nature Cell Biol.* **11**, 328–336 (2009).
42. Gerdes, H. H. & Carvalho, R. N. Intercellular transfer mediated by tunneling nanotubes. *Curr. Opin. Cell Biol.* **20**, 470–475 (2008).
43. Li, J. Y. *et al.* Lewy bodies in grafted neurons in subjects with Parkinson's disease suggest host-to-graft disease propagation. *Nature Med.* **14**, 501–503 (2008).
44. Kordower, J. H., Chu, Y., Hauser, R. A., Olanow, C. W. & Freeman, T. B. Transplanted dopaminergic neurons develop PD pathologic changes: a second case report. *Mov. Disord.* **23**, 2303–2306 (2008).
45. Kordower, J. H., Chu, Y., Hauser, R. A., Freeman, T. B. & Olanow, C. W. Lewy body-like pathology in long-term embryonic nigral transplants in Parkinson's disease. *Nature Med.* **14**, 504–506 (2008).
46. Desplats, P. *et al.* Inclusion formation and neuronal cell death through neuron-to-neuron transmission of α-synuclein. *Proc. Natl Acad. Sci. USA* **106**, 13010–13015 (2009).
47. Yang, W., Dunlap, J. R., Andrews, R. B. & Wetzel, R. Aggregated polyglutamine peptides delivered to nuclei are toxic to mammalian cells. *Hum. Mol. Genet.* **11**, 2905–2917 (2002).
48. Lee, H. J. *et al.* Assembly-dependent endocytosis and clearance of extracellular α-synuclein. *Int. J. Biochem. Cell Biol.* **40**, 1835–1849 (2008).
49. Frost, B., Jacks, R. L. & Diamond, M. I. Propagation of tau misfolding from the outside to the inside of a cell. *J. Biol. Chem.* **284**, 12845–12852 (2009).
50. Ren, P. H. *et al.* Cytoplasmic penetration and persistent infection of mammalian cells by polyglutamine aggregates. *Nature Cell Biol.* **11**, 219–225 (2009).
51. Krammer, C. *et al.* The yeast Sup35NM domain propagates as a prion in mammalian cells. *Proc. Natl Acad. Sci. USA* **106**, 462–467 (2009).
52. Meyer-Luehmann, M. *et al.* Exogenous induction of cerebral β-amyloidogenesis is governed by agent and host. *Science* **313**, 1781–1784 (2006).
53. Clavaguera, F. *et al.* Transmission and spreading of tauopathy in transgenic mouse brain. *Nature Cell Biol.* **11**, 909–913 (2009).
54. Werdelin, O. & Ranlov, P. Amyloidosis in mice produced by transplantation of spleen cells from casein-treated mice. *Acta Pathol. Microbiol. Scand.* **68**, 1–18 (1966).
55. Westermark, G. T. & Westermark, P. Serum amyloid A and protein AA: molecular mechanisms of a transmissible amyloidosis. *FEBS Lett.* **583**, 2685–2690 (2009).
56. Lundmark, K. *et al.* Transmissibility of systemic amyloidosis by a prion-like mechanism. *Proc. Natl Acad. Sci. USA* **99**, 6979–6984 (2002).
57. Mendez, O. E., Shang, J., Jungreis, C. A. & Kaufer, D. I. Diffusion-weighted MRI in Creutzfeldt-Jakob disease: a better diagnostic marker than CSF protein 14-3-3? *J. Neuroimaging* **13**, 147–151 (2003).
58. Asuni, A. A., Boutajangout, A., Quartermain, D. & Sigurdsson, E. M. Immunotherapy targeting pathological tau conformers in a tangle mouse model reduces brain pathology with associated functional improvements. *J. Neurosci.* **27**, 9115–9129 (2007).
59. Masliah, E. *et al.* Effects of α-synuclein immunization in a mouse model of Parkinson's disease. *Neuron* **46**, 857–868 (2005).
60. Nekooki-Machida, Y. *et al.* Distinct conformations of *in vitro* and *in vivo* amyloids of huntingtin-exon1 show different cytotoxicity. *Proc. Natl Acad. Sci. USA* **106**, 9679–9684 (2009).

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Competing interests statement

The authors declare no competing financial interests.

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FURTHER INFORMATION

Marc I. Diamond's homepage: http://neuro.wustl.edu/research/researchlabs/diamondlaboratory.htm

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