Biology and Genetics of PrP Prion Strains

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Prion diseases are a group of fatal neurodegenerative disorders caused by the misfolding of the cellular prion protein (PrP^C) into a pathogenic conformation (PrP^{Sc}). PrP^{Sc} is capable of folding into multiple self-replicating prion strains that produce phenotypically distinct neurological disorders. Evidence suggests that the structural heterogeneity of PrP^{Sc} is the molecular basis of strain-specific prion properties. The self-templating of PrP^{Sc} typically ensures that prion strains breed true upon passage. However, prion strains also have the capacity to conformationally transform to maximize their rate of replication in a given environment. Here, we provide an overview of the prion-strain phenomenon and describe the role of strain adaptation in drug resistance. We also describe recent evidence that shows the presence of distinct conformational strains in other neurodegenerative disorders.

The term "prion disease" has historically been used to denote a group of fatal neurodegenerative diseases caused by misfolding of the prion protein (PrP) (Prusiner 1982, 2001, 2013; Colby and Prusiner 2011). These disorders occur in a number of mammals and include Creutzfeldt–Jakob disease (CJD) in humans, bovine spongiform encephalopathy (BSE) in cattle, scrapie in sheep, and chronic wasting disease (CWD) in cervids. A key feature in the etiology of these diseases is the self-templating and propagation of pathogenic conformations of PrP. Although the phenomenon of templated propagation was initially described for PrP-based prion diseases, recent experiments have indicated that aggregates of proteins causing other common neurodegenerative disorders can also stimulate the formation of pathogenic protein conformations in vivo (Meyer-Luehmann et al. 2006; Kordower et al. 2008; Clavaguera et al. 2009; Desplats et al. 2009; Eisele et al. 2009; Frost et al. 2009; Ren et al. 2009; Prusiner 2012). Thus, the term "prion disease" can now be more broadly applied to a range of common neurodegenerative disorders, including Alzheimer's (AD), Parkinson's (PD), and Huntington's diseases.

Many features associated with the propagation of PrP-based prions, including templated seeding and cell-to-cell transmission, have now been observed in non-PrP prions. Another important property of classical PrP prions that has recently been shown in AD and PD is the occurrence of distinct phenotypic strains with unique conformational and biochemical properties (Prusiner 2013; Le et al. 2014; Stohr et al. 2014; Watts et al. 2014; Morales et al. 2015). In this review, we provide an overview of the prion-strain phenomenon and outline recent evidence that suggests that distinct conformational strains are also present in AD and PD. We will also describe the ramifications of the strain

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phenomenon for understanding the pathology of neurodegenerative disorders and the development of effective therapeutics.

THE PRION-STRAIN PHENOMENON

The neuropathological features of PrP-based prion diseases are thought to be initiated by misfolding of endogenous cellular PrP (PrP^C) into a disease-associated infectious aggregate (PrP^{Sc}). This conversion can occur spontaneously, it can be induced by the presence of genetic mutations in the gene encoding PrP^C, or it can be incurred by intake of PrP^{Sc} from outside sources. These three modes of origination account for the sporadic, genetic, and infectious forms of PrP-based prion diseases, respectively. The ability of PrP^{Sc} to act as an infectious particle is due to its capacity to stimulate its own creation in a chain reaction that uses natural PrP^C as a substrate (a process that is often referred to as "templating" or "seeding"). Once the conversion process is initiated, the subsequent formation of PrP^{Sc} occurs with exponential kinetics, resulting in the accumulation of a conformationally heterogeneous population of prion aggregates in infected tissues (Colby and Prusiner 2011; Prusiner 2013).

The strain phenomenon is a concept that was initially invoked to describe the ability of prion diseases to show multiple distinguishable phenotypes. At first, the existence of prion strains was thought to be at odds with the protein-only hypothesis, as it was unclear how the misfolding of a single protein could result in multiple and diverse disease outcomes (Soto and Castilla 2004). However, it is now known that variations in phenotypic features of prion strains can be accounted for by heterogeneities in the structural and biochemical features of PrP^{Sc} (Bessen et al. 1995; Telling et al. 1996; Tanaka et al. 2004; Morales et al. 2007). Thus, the ability of a single PrP polypeptide chain to misfold into multiple conformations accounts for the prevalence of multiple infectious states with distinguishable disease phenotypes.

The prion-strain phenomenon was first described for scrapie when it was shown that the infectious agent could be propagated in goats as multiple phenotypically distinct entities (Pattison and Jones 1967; Dickinson and Meikle 1969). These studies indicated that goats infected with the same batch of the scrapie inoculum could develop prion disease with two distinct clinical features, termed "scratching" and "drowsy." Subsequent studies in mice showed that animals inoculated with different scrapie strains display distinct incubation periods and histopathologies, and that these characteristics are propagated with fidelity on serial passage (Fraser and Dickinson 1973). These early studies distinguished prion strains in terms of phenotypic features of the disease, such as incubation times and neuropathological profiles. However, it soon became clear that the phenotypic diversity of prion strains could also be observed in terms of the biochemical and structural properties of the pathogenic agent. For example, the characterization of two biologically distinct strains of hamster-adapted transmissible mink encephalopathy (TME) prions, hyper (HY) and drowsy (DY), indicated that the protease-resistant cores of their corresponding PrP^{Sc} structures differed in electrophoretic mobility in denaturing gels (Bessen and Marsh 1992). This shift in mobility suggested that different prion strains have different three-dimensional conformations that expose different parts of the structure to proteases.

Other lines of evidence for the prion-strain concept came from studies of human prion diseases. Fatal familial insomnia (FFI) is a genetic prion disease caused by a mutation of an aspartic acid to an asparagine at position 178 of PrP (D178N) (Goldfarb et al. 1992; Medori et al. 1992; Monari et al. 1994). PrP^{Sc} aggregates associated with FFI were shown to have different electrophoretic mobility when compared with sporadic CJD (sCJD). Furthermore, it was shown that an M/V polymorphic mutation at position 129 of PrP modulates the effects of the D178N mutation on both the conformation of PrP^{Sc} and disease phenotype. These observations led to the suggestion that differences in disease outcomes can be associated with differences in the conformation of PrP^{Sc}. Subsequent experiments showed that these strain-specific

properties could be faithfully propagated in transgenic mice infected with human-derived inocula (Telling et al. 1996).

An important recent advance in understanding the biochemical nature of prion-strain diversity has stemmed from the creation of infectious synthetic prions formed exclusively from bacterially derived recombinant PrP (Legname et al. 2004, 2005; Colby et al. 2010; Makarava et al. 2010). Synthetic prion strains can be created by refolding recombinant PrP into β-sheet-rich amyloid fibrils, followed by intracerebral inoculation into mice. Passage of these synthetic strains into groups of mice results in diverse incubation times, and these properties can be faithfully propagated upon subsequent passage. Results from these studies suggest that the initial synthetic inoculum consists of multiple distinct strains that become "isolated" upon passage (Colby et al. 2009, 2010). Studies have highlighted the ability of PrP^{Sc} to act as a structural template in directing the formation of nascent PrP^{Sc} and have provided further evidence that prion-strain diversity is encrypted in the conformation of PrP^{Sc}.

TECHNIQUES FOR BIOCHEMICAL CHARACTERIZATION OF PrP-BASED PRION STRAINS

Due to their aggregated conformation, PrP^{Sc} strains have structural properties that have been historically difficult to investigate at atomic resolutions. Instead, to differentiate prion strains, researchers often infer strain-specific conformational differences based on low-resolution biochemical characteristics of PrP^{Sc}. Perhaps the most frequently used method for distinguishing prion strains has been the electrophoretic mobility of PrP^{Sc} after digestion by proteinase K (PK) (Bessen and Marsh 1992). The formation of PrP^{Sc} results in an aggregated conformation that renders a portion of the protein resistant to proteolysis. Variations in the size of the protease-resistant core are suggestive of changes in the higher-order structure of PrP^{Sc}. Other low-resolution biochemical techniques for analysis of prion strains include determining the glycosylation pattern of PrP^{Sc}, the

extent of protease resistance, and the rates of sedimentation.

The above approaches have provided convincing evidence that phenotypic differences in prion strains are due to structural differences in PrP^{Sc}. However, the low-resolution nature of these techniques has made it difficult to assess the full range of conformational strains. For example, it has been difficult to assess whether a specific PrP^{Sc} PK-digested banding pattern is indicative of a single conformation or an ensemble of conformations with similarly sized protease-resistant cores. More recent biochemical techniques, including conformational dependent immunoassay (CDI) (Safar et al. 1998), differential affinities toward conjugated polymers (Sigurdson et al. 2007), propensity to infect specific cell lines (Mahal et al. 2007), and quantitative analysis of conformational stabilities (Peretz et al. 2001), have provided a higher-resolution picture of strain-specific conformational properties. CDI, in particular, has been pivotal in providing the first sensitive conformation-dependent assay for detecting diverse strains. This assay quantitates the binding of antibodies to the denatured and native forms of PrP^{Sc}. Subtle structural differences between strains impacts the binding of the antibody to native PrP^{Sc} to different extents. Thus, CDI can provide quantitative measures of binding profiles of the antibody to each strain. CDI and other high-resolution biochemical techniques have provided strong evidence that PrP^{Sc} can potentially take on a large number of pathogenic conformations. These studies have led to the remarkable conclusion that rather than constituting a small number of discrete states, prion strains are likely composed of a continuous spectrum of conformations with potentially distinct phenotypes.

RELATIONSHIP BETWEEN CONFORMATIONAL STABILITIES AND REPLICATION RATES OF PRION STRAINS

What accounts for the ability of PrP^{Sc} to adopt multiple, phenotypically distinct conformations? It is likely that all prion strains adopt cross-β amyloid conformations with varying

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steric architectures (Del Mar et al. 2005; Nelson et al. 2005; Chiti and Dobson 2006; Wiltzius et al. 2009). The conformational heterogeneity of prions may thus arise from differences in the intermolecular register and packing of side chains. Subtle structural differences between strains can potentially alter biophysical properties that impact the rate of prion propagation in a given cellular environment. For example, conformational differences between strains can potentially alter the kinetics of PrP^C–PrP^{Sc} interaction, conformational conversion, and fiber fragmentation. These differences may enable specific prion strains to more efficiently convert PrP^C substrates with specific primary sequences and/or within specific cellular environments.

One specific biophysical characteristic of prion strains that has been found to strongly correlate with rates of propagation and incubation periods is conformational stability. Analysis of a large number of prion isolates indicates that the concentration of chaotrope guanidinium-hydrochloride (Gdn.HCl) required to denature PrP^{Sc} molecules is negatively correlated with incubation periods (Legname et al. 2006). One possible molecular explanation for this trend is that the denaturation curve of PrP^{Sc} is an indicator of its ability to fragment and create additional catalytic ends for the conversion of PrP^C. Thus, a prion strain with lower stability has an increased tendency to become fragmented, resulting in increased rates of PrP^{Sc} formation and shorter incubation periods. Additional support for this idea has come from studies of infectious synthetic prions created under different in vitro conditions in which the conformational stabilities of the amyloid inocula correlate with the infectivity of the prion strains induced in vivo (Colby et al. 2009).

Interestingly, a similar correlation between prion stability and propagation has been observed in yeast prion strains (Tanaka et al. 2004). In yeast Sup35 prions, the most rapidly propagating strains are amyloid fibrils, which have the highest tendency to fragment. Indeed, it has been shown that enhanced fragility of yeast prions can more than compensate for deceased templating efficiencies. Additional support for the importance of fibril brittleness in

prion propagation has come from cell-free fiber formation assays where induction of fiber breakage increases rates of new fiber formation (Baskakov and Breydo 2007). Together, these data suggest that the variability in the conformational stability of prion aggregates plays a large role in dictating the rates of prion propagation and degrees of infectivity. However, it should be noted that some contrary evidence to this trend has been observed in hamster-adapted strains, suggesting that factors other than stability may contribute to the propagation rate of prion strains (Ayers et al. 2011).

PRION-STRAIN ADAPTATION

Early studies of prion strains highlighted the ability of prion strains to breed true upon serial passage. However, a number of subsequent observations have shown that prion strains are capable of altering their conformation to adapt to new hosts and environments in a process referred to as "strain adaptation." The process of strain adaptation is frequently observed when prions cross the species barrier. The transmission of prions across species is highly inefficient. Interspecies transmissions are often characterized by long incubation times and low infection rates (Kimberlin and Walker 1986; Scott et al. 1989, 1993; Prusiner et al. 1990). Evidence suggests that this species barrier is a result of incompatibilities between the conformations of the infecting prion strain and host PrP^C, owing in part to differences in the amino-acid sequences. However, upon repeated passage, the prion conformation changes in its new host, and the incubation period gradually shortens.

The process of prion-strain adaptation has also been observed as gradual interconversions of strains originating from the same organism (without crossing a species barrier). For example, as described above, passage of biologically cloned TME prions in hamsters results in two phenotypically distinct strains: DY and HY. The former strain has a characteristically long incubation period, whereas the latter has a short incubation period (Bessen and Marsh 1992). Upon initial infection of hamsters with cloned TME, the DY strain predominates. However, af-

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ter continuous serial passage, the HY strain gradually becomes the dominant strain (Bessen and Marsh 1992; Bartz et al. 2000; Schutt and Bartz 2008).

A similar phenomenon has been observed in mice infected with variant CJD (vCJD) strains. Transgenic mice expressing chimeric human/mouse PrP inoculated with vCJD prions can harbor two distinct strains of prions. In mice that express a mixture of the two strains, the faster replicating strain becomes dominant on continuous passage (Giles et al. 2010).

The phenomenon of strain adaptation has also been shown in synthetic PrP^{Sc} strains upon serial transmission in mice. When amyloid fibrils formed from purified recombinant PrP are used to infect transgenic mice, the incubation periods of the resulting synthetic strains gradually shorten upon passage (Ghaemmaghami et al. 2011, 2013). This increase in infectivity is accompanied by a structural transformation of PrP^{Sc} as indicated by a shift in the molecular mass of the protease-resistant core and a decrease in conformational stability. This process of strain adaptation is also observed when synthetic prions are propagated in cultured cell lines (Ghaemmaghami et al. 2011).

A similar phenomenon of strain adaptation has been observed in hamsters infected with synthetic prions. These animals are asymptomatic at first passage and initially accumulate PrP^{Sc} with atypical banding patterns. However, subsequent passage leads to the appearance of typical PrP^{Sc} (Makarava et al. 2010, 2011, 2012). Together, these studies show that prions can readily alter their conformation to maximize their rate of replication in a given cellular environment.

Most natural strains are stable and can propagate with a high degree of conformational fidelity over many rounds of passage. If prion strains are conformationally adaptable, why don't all strains gradually transform to a single optimized state upon repeated passage? The conformational landscape of a prion, shaped by the primary sequence of the prion protein, likely encompasses a large number of local energy minima that can indefinitely trap structures that are not at the global energy minimum (Weissmann et al. 2011). According to this model, the localization of the prion conformation on the energy landscape will determine whether the strain is biologically stable or transient.

THE MECHANISM OF PRION-STRAIN ADAPTATION

What is the structural basis of prion strain diversity? Prions belong to the amyloid class of filamentous protein aggregates. As a group, amyloid fibrils are rich in β-sheet secondary structures and are formed by the noncovalent stacking of polypeptide chains aligned in a cross-β configuration. However, the exact structural orientation of β-sheets can vary between different amyloid structures. A number of amyloid stacking arrangements have been described, including parallel in-register β-sheets, antiparallel β-sheets, and β-helices (Del Mar et al. 2005; Nelson et al. 2005; Chiti and Dobson 2006; Wiltzius et al. 2009). Additionally, the structure of the interlocking self-complementary surfaces of adjacent β-sheets can vary between different amyloids. The structural heterogeneity in conformations of amyloids is the likely basis of prion-strain diversity. It is thought that the conformational constraints of specific amyloid structures ensure that monomers being incorporated at the ends of the growing fiber conform to the unique structural features of each strain. Although the high fidelity of prion-strain replication is well documented, it is possible that deformed templating events (Makarava et al. 2012) occur in rare instances. Such events can result in a conformational alteration at the catalytic ends of a growing amyloid fiber that can be propagated in further rounds of monomer addition. Alternatively, prion strains may have the capacity to convert to structurally distinct self-templating strains in a stochastic process that is not strictly dependent on faulty monomer addition (Collinge and Clarke 2007). Thus, PrP^{Sc} aggregates may have the ability to interconvert between different conformations that can subsequently replicate with fidelity. The constant conformational drift of replicating prions can continuously produce pools of struc-

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turally distinct self-replicating prions that can be acted upon by conformational selection.

Within a complex mixture of prion conformations, faster replicating strains are expected to increase their relative population over time. The rate of this selective process can be further amplified by the phenomenon of strain interference. Coexisting prion strains can influence the replication of each other by competing for a limited supply of resources required for amplification. As a mixture, coexisting strains are competing for the same pool of PrP^C substrate and other auxiliary factors that may be required for PrP^{Sc} formation. Adapted strains that are more effective at interacting with PrP^C or other auxiliary factors may deny other strains the resources required for their propagation. The phenomenon of prion-strain interference has been described for a wide variety of prion strains (Dickinson et al. 1972; Bartz et al. 2004; Schutt and Bartz 2008; Shikiya et al. 2010). For example, infection with the HY strain of TME can be inhibited by co-inoculation with the TME DY strain. The results suggest that DY and HY can compete for a limited cellular resource. The combination of spontaneous conformational mutations and strain interference provides a potent mechanism for rapid adaptation of prion strains.

PRION STRAINS AND DRUG RESISTANCE

The availability of robust in vitro and in vivo models for prion disease has resulted in the identification of a number of small molecules that induce the clearance of PrP^{Sc} (Trevitt and Collinge 2006; Sim 2012). However, many inhibitors of prion propagation display strain specificity and can be effective against some strains and not others (Adjou et al. 1996; Demaimay et al. 1999; Doh-ura et al. 2004; Kocisko et al. 2005; Kawasaki et al. 2007; Berry et al. 2013). This phenomenon has been observed in both cell culture and animal models of the disease. Given that the exact mechanisms of action for most antiprion compounds are incompletely understood, it has been difficult to ascertain the exact molecular basis of drug-strain specificity. For compounds that exert their effect by

direct interaction with PrP^{Sc}, such strain specificity may derive from conformational differences in PrP^{Sc} that influence the binding of the compound to the aggregate. For compounds that indirectly influence prion propagation by affecting auxiliary pathways or other cofactors, strain specificity may be indicative of the relative dependence of the propagation of a given strain on that specific pathway or cofactor.

The fact that antiprion compounds can be strain-specific and that prion strains have the ability to conformationally adapt to maximize their rates of replication has given prions the capacity to evade the actions of antiprion drugs. This drug-resistance phenomenon has recently been shown in experiments involving three drugs targeting mammalian prions: quinacrine, swainsonine, and aminothiazoles.

Quinacrine

Quinacrine's antiprion activity was initially reported by two independent studies in prion-infected neuronal cell-culture systems (Doh-Ura et al. 2000; Korth et al. 2001). Incubation of prion-infected cells with quinacrine induces the clearance of protease-resistant PrP^{Sc}. A subsequent study using bis-acridine compounds that comprise two acridine ring scaffolds connected by a linker showed the improved potency of this class of therapeutics (May et al. 2003). Despite its promise in cell-culture models, quinacrine has not proven effective in mouse models or human clinical trials (Collins et al. 2002; Barret et al. 2003; Nakajima et al. 2004; Collinge et al. 2009; Ghaemmaghami et al. 2009; Geschwind et al. 2013). In MDR1$^{0/0}$ mice lacking ATP-binding cassette (ABC) transporter P-glycoprotein (Pgp), quinacrine accumulates in the brain at levels that exceed its in vitro effective concentration by a factor of 100 (Ghaemmaghami et al. 2009). However, despite its excess accumulation, quinacrine does not significantly increase the life span of prion infected mice even when drug administration is initiated shortly after inoculation (Ghaemmaghami et al. 2009).

Follow-up biochemical analyses of brain homogenates collected from drug-treated pri-

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on-infected mice provided evidence for the gradual accumulation of drug-resistant strains (Ghaemmaghami et al. 2009). Prion levels in the brains of infected mice initially diminish upon quinacrine treatment. However, this reduction is transient, and PrP^{Sc} levels rebound as the drug is continually administered. The results suggest that chronic quinacrine treatment leads to the proliferation of resistant prion strains that survive the initial treatment. Furthermore, it was shown that PrP^{Sc} accumulated in the brains of chronically treated mice had an altered conformational stability. The formation of quinacrine-resistant prions was also observed in infected cultured cells upon the arrest of cell division.

Swainsonine

Swainsonine is an inhibitor of Golgi α-mannosidase II (Tulsiani et al. 1982) and inhibits the replication of specific prion strains by blocking the N-glycan processing of PrP (Li et al. 2010). Upon treating a panel of prion-infected cell lines with swainsonine, the Weissmann group observed prion-strain adaptation and resistance to the drug in different environments (Li et al. 2010). This initial observation led to a number of follow-up studies exploring changes in prion-strain characteristics when subjected to different environments and treatments (Li et al. 2010, 2011; Mahal et al. 2010; Browning et al. 2011; Oelschlegel and Weissmann 2013). The results of these studies led to an elegant model describing the mechanism of swainsonine resistance. A small fraction of the normal prion population is inherently swainsonine resistant, and this resistant population is selectively amplified in the presence of the drug. Once the selective pressure of the drug is removed, swainsonine-sensitive prion conformations become the dominant species once again.

Aminothiazoles

In 2010, a large cell-based screen led to the identification of a novel class of antiprion drugs with the 2-aminothiazole (AMT) chemical backbone (Ghaemmaghami et al. 2010). Follow-up structure–activity relationship (SAR) studies led to the development of highly potent compounds with favorable pharmacokinetic properties (Gallardo-Godoy et al. 2011; Li et al. 2013; Silber et al. 2013). Subsequently, the in vivo efficacy of two analog compounds with the AMT backbone was evaluated in mouse models (Berry et al. 2013). Oral administration of both compounds was found to significantly extend the survival of mice infected with a number of prion strains (e.g., RML, ME7, and CWD). Importantly, significant extensions of life span were observed when drug treatment was initiated late in the course of disease (e.g., 60 days postinoculation). Despite a significant and reproducible extension of life span in these studies, AMT-treated mice eventually showed accumulation of PrP^{Sc} in their brains and ultimately succumbed to disease. Even more disappointing, the aminothiazoles proved ineffective against human Creutzfeldt–Jakob disease prions in susceptible transgenic mice expressing human PrP^{C}.

The above studies indicate that the efficacy of AMTs is strain-specific. Importantly, in a number of detailed experiments, it was shown that the failure of AMTs is a result of induction of drug-resistant strains. Prions isolated from the brains of terminal AMT-treated scrapie-infected mice were resistant to AMTs when propagated in cell culture. The studies also revealed that selective drug pressure must be continuously maintained in vivo to preserve the resistant strain. This observation may suggest that AMT treatment results in the selection and proliferation of a resistant prion strain that is otherwise less proliferative than drug-sensitive strains.

The observation that three independent antiprion drugs (quinicarine, swainsonine, and aminothiazoles) induce the formation of drug-resistant strains suggests that drug resistance may be a general confounding problem for the development of antiprion therapeutics. This highlights the urgent need for the development of cell models infected with human prions and a more target-oriented drug discovery effort to circumvent the problem of drug resistance. For example, targeting of PrP^{C}, the en-

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dogenous substrate shared by all prion strains, is more likely to identify compounds that have broad strain specificity. Additionally, more sophisticated dosing regiments involving combinations of diverse drugs and intermittent dosing may be required to avoid drug resistance.

PRION STRAINS IN NON-PrP NEURODEGENERATIVE DISORDERS

Recent findings have shown that several misfolded proteins can transmit pathogenesis in a conformationally templated manner that is analogous to PrP. Several lines of research have shown that many well-known features of prions are present in Aβ, α-synuclein, and tau aggregates (Meyer-Luehmann et al. 2006; Kordower et al. 2008; Clavaguera et al. 2009; Desplats et al. 2009; Eisele et al. 2009; Frost et al. 2009; Ren et al. 2009; Prusiner 2012). Among these shared features is the presence of conformational strains with distinct structural and phenotypic characteristics. Importantly, the presence of diverse prion strains associated with Aβ, α-synuclein, and tau provides a molecular basis for clinical and pathological heterogeneity in AD, PD, and other tauopathies. Below we describe recent experimental evidence for the presence of non-PrP prion strains.

Aβ Prion Strains

Strong evidence for the presence of Aβ strains has been obtained by infecting mice with aggregates obtained from patients with sporadic and familial (Arctic and Swedish) AD (Watts et al. 2014). Aβ in patients was shown to have different conformational stabilities and patterns of plaque deposition. Inocula from each patient group resulted in different incubation periods in infected animals. Mice inoculated with the Arctic AD sample showed a pathology distinguishable from mice inoculated with the Swedish or sporadic AD samples. Specifically, the accumulation of Aβ isoforms and the morphology of cerebrovascular Aβ deposition differed between the two groups of inoculated mice. Remarkably, these features were maintained after a second round of passage. Additional studies showed that different aggregation profiles (e.g., $A\beta_{40}/A\beta_{42}$ ratio and compactness of plaques) are observed after inoculation of mice with synthetic Aβ fibrils formed in vitro in the presence or absence of a detergent (Stöhr et al. 2014). These studies, and other experiments conducted in APP23 mice (Meyer-Luehmann et al. 2006; Heilbronner et al. 2013), provide strong support for the presence of distinct transmissible Aβ strains in AD.

Tau Prion Strains

Strain variations have also been documented for tau aggregates. Transgenic mice infected with inocula derived from human patients afflicted with various tauopathies generated tau pathology reminiscent of the original inoculum (Clavaguera et al. 2009). Remarkably, aggregates generated after the initial transmission were able to seed endogenous mouse tau in wild-type animals. However, the serial propagation of the strain-specific properties in these mice or in new transgenic animals was not reported.

Additional support for the tau strains has come from studies in cell-culture models (Sanders et al. 2014). Cells harboring tau aggregates were classified in terms of the morphology of the generated aggregates. Two tau strains were characterized and were subsequently shown to have varying degrees of seeding efficiencies in vitro, toxicity profiles, and subcellular localizations. These strain-specific characteristics were faithfully propagated in inoculated cells. Furthermore, the specific characteristics of each tau strain were maintained in transgenic mice inoculated with each strain.

α-Synuclein Prion Strains

A number of recent studies have shown that synthetic α-synuclein fibrils can transmit disease in vivo, lead to cell-to-cell transmission of protein aggregates, and induce PD-like pathologies (Braak et al. 2003; Luk et al. 2012; Masuda-Suzukake et al. 2013). Support for the existence of α-synuclein strains has come from studies by Bousset et al. (2013). This group has generated two assemblies of α-synuclein aggre-

gates with different propensities for binding and penetrating cells. These aggregates can propagate their structures by acting as a template for endogenous α-synuclein. Other work by Guo et al. (2013) has characterized two distinct strains of synthetic α-synuclein fibrils that show striking differences in the efficiency of cross-seeding tau aggregation, both in neuron cultures and in vivo. Additionally, Watts et al. (2013) have shown that brain homogenates prepared from multiple system atrophy (MSA) patients or mouse models induced disease in infected mice. The two inocula were transmitted at different rates, suggesting that the α-synuclein aggregates constitute distinct strains. More recent evidence indicates that the MSA strains are distinct from PD-causing prions (Prusiner et al. 2015).

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