β -Amyloid Prions and the Pathobiology of Alzheimer's Disease

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Alzheimer's disease (AD) is the most common neurodegenerative disease in humans and will pose a considerable challenge to healthcare systems in the coming years. Aggregation of the β -amyloid (A β) peptide within the brain is thought to be an initiating event in AD pathogenesis. Many recent studies in transgenic mice have provided evidence that A β aggregates become self-propagating during disease, leading to a cascade of protein aggregation in the brain, which may underlie the progressive nature of AD. The ability to self-propagate and the existence of distinct "strains" reveals that A β aggregates exhibit many properties indistinguishable from those of prions composed of PrP^{Sc} proteins. Here, we review the evidence that A β can become a prion during disease and discuss how A β prions may be important for understanding the pathobiology of AD.

Alzheimer's disease (AD) is the most common cause of dementia in humans and is most frequently diagnosed in individuals 65 yr of age or older. The incidence of AD varies with age: about one in nine people age 65 or older will develop AD, whereas about one in three individuals age 85 or older will be diagnosed with the disease (Hebert et al. 2013). Early-onset cases of AD, which occur in individuals younger than age 65, are comparatively rare and include familial cases caused by mutations in genes linked to the production of the β -amyloid (A β) peptide. The predominant clinical symptoms of AD are cognitive deficits and behavioral changes. AD patients typically first present with difficulties in remembering recent

occurrences, but with intact memories of older events. The earliest, predementia stages of the disease are often classified clinically as mild cognitive impairment, which describes the presence of memory problems greater than those expected from normal aging. As the disease progresses, additional symptoms become apparent, which may include problems with language, confusion, mood swings, long-term memory loss, and withdrawal from society. Eventually, AD patients become completely dependent on caregiver assistance. There are currently no cures or effective treatments for AD. Although available treatments may temporarily improve behavioral problems, they do not address the root cause of the disease or its progression.

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Figure 1. Generation of β -amyloid ($A\beta$) peptide via endoproteolytic cleavage of amyloid precursor protein (APP). The mature form of the longest isoform of human APP (following removal of an N-terminal signal peptide) spans residues 18–770. In the amyloidogenic pathway, cleavage of the APP extracellular domain by β -secretase produces a secreted fragment termed sAPP β and a membrane-embedded C-terminal fragment called C99. Cleavage of C99 by γ -secretase produces the APP intracellular domain (AICD) and the $A\beta$ peptide. Cleavage of APP by γ -secretase is heterogeneous, resulting in the generation of $A\beta$ peptides that vary in length between 37 and 43 residues.

AD is a progressive neurodegenerative disease of aging. The brains of AD patients exhibit a remarkable loss of synapses and neurons, which results in an overall shrinkage of the brain, particularly in the temporal and parietal lobes as well as in the frontal cortex. At the microscopic level, two principal pathologies are observed: amyloid (senile) plaques and neurofibrillary tangles (NFTs). The dense, extracellular amyloid plaques are composed of aggregated $A\beta$ peptide, whereas the intracellular NFTs are made up of paired helical filaments of hyperphosphorylated tau protein. $A\beta$ is generated by the sequential endoproteolytic cleavage of the amyloid precursor protein (APP), a Type-1 transmembrane protein that exists as three different isoforms with lengths

of 695, 751, and 770 amino acids. In the amyloidogenic processing pathway, APP is cleaved by two different proteases: β -secretase and γ -secretase (Fig. 1). β -Secretase first cleaves the extracellular juxtamembrane region of APP, resulting in a membrane-embedded fragment termed C99. The transmembrane portion of C99 is then cleaved by γ -secretase, a multiprotein complex that includes the enzymatically active presenilin proteins (De Strooper et al. 2012), freeing the $A\beta$ peptide. Cleavage of C99 by γ -secretase is heterogeneous in nature and results in the generation of $A\beta$ peptides varying in length from 37 to 43 amino acids (Benilova et al. 2012). If APP is first cleaved by α -secretase instead of β -secretase, the generation of $A\beta$ is prevented.

The amyloid cascade hypothesis, which is the most widely accepted theory for the molecular sequence of events in AD, postulates that the initiating event in AD is the aggregation and subsequent deposition of A β peptide in the brain (Hardy and Selkoe 2002). This results in the hyperphosphorylation and polymerization of tau into NFTs and, ultimately, degeneration of neurons. This hypothesis is supported by the following observations: (1) Mutations in the gene encoding APP cause early-onset forms of AD and increase the production of A β or enhance its aggregation potential (Chartier-Harlin et al. 1991; Citron et al. 1992); (2) duplication of the APP coding locus results in early-onset AD (Rovelet-Lecrux et al. 2006); (3) in Down's syndrome patients, an extra copy of chromosome 21, which contains the *APP* gene, invariably causes AD-like pathological changes in the brain (Wisniewski et al. 1985); (4) mutations in the *APP* gene that decrease A β production are protective against AD (Jonsson et al. 2012); and (5) mutations in the genes encoding the presenilin proteins increase the relative abundance of pro-amyloidogenic A β isoforms and cause early-onset AD (Sherrington et al. 1995). Thus, increased A β production and deposition in the brain is sufficient to cause AD, suggesting that A β aggregation is central to AD pathogenesis. In contrast, mutations in the gene encoding tau result in the production of NFTs in the brain (Hutton et al. 1998; Spillantini et al. 1998), but not amyloid plaques. Such patients develop a tauopathy termed FTDP-17 that is clinically and pathologically distinct from AD, revealing that tau mutations are insufficient to elicit the full neuropathological spectrum observed in AD.

MOUSE MODELS OF ALZHEIMER'S DISEASE

Transgenic (Tg) mice that overexpress mutant human APP containing one or more mutations that cause early-onset, familial forms of AD develop A β -containing amyloid plaques with aging (Morrisette et al. 2009). These mice, referred to hereafter as Tg(AD) mice, thus recapitulate one of the key neuropathological hallmarks of AD. The kinetics of A β deposition in Tg(AD) mice is governed by the relative level of

APP overexpression as well as the specific mutations present. For example, Tg2576 mice expressing human APP containing the Swedish mutation (K670N/M671L) (Citron et al. 1992; Mullan et al. 1992), which causes enhanced cleavage of APP by β -secretase (Haass et al. 1995) and, consequently, increased A β production, develop A β plaques beginning at $\sim$ 12 mo of age (Hsiao et al. 1996). In contrast, TgCRND8 mice expressing a mutant APP allele containing the Swedish mutation and the Indiana mutation (V717F) (Murrell et al. 1991), which increases the relative abundance of the more aggregation-prone A β 42 isoform (Suzuki et al. 1994), develop amyloid plaques at $\sim$ 3–4 mo of age (Chishti et al. 2001).

Some lines of Tg(AD) mice exhibit age-dependent memory impairment, mimicking the cognitive deficits observed in AD patients, and exhibit some tau hyperphosphorylation (for review, see Morrisette et al. 2009). Moreover, the cerebrospinal fluid (CSF) of Tg(AD) mice contains increased levels of tau and decreased levels of A β 42 peptide, mirroring the biomarker signature of individuals with AD (Maia et al. 2013). These data support the translational utility of Tg(AD) mice. Indeed, these animals have been used to show that reducing levels of A β aggregates in the brain, either by vaccination or passive immunotherapy, can rescue cognitive deficits (Schenk et al. 1999; Bard et al. 2000; Janus et al. 2000). However, current Tg(AD) mice do not constitute an ideal animal model of AD because, unlike AD patients, Tg(AD) mice do not develop NFTs in response to A β aggregation and do not display frank neuronal loss (Jucker 2010).

Tg(AD) mice do not exhibit overt progressive clinical signs of neurological illness with aging, despite the presence of abundant A β plaques. Thus, the only way of assessing the kinetics of A β deposition in the brain is to perform postmortem analysis of fixed tissue using neuropathological techniques. This is not ideal for several reasons. First, this greatly increases the number of animals needed for a study, as separate cohorts are required for each time point under investigation. Second, it necessitates “guessing” when A β deposition is expect-

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Figure 2. Monitoring spontaneous and induced A β deposition in bigenic mice using in vivo bioluminescence imaging (BLI). The brain BLI signal in bigenic Tg(APP23:Gfap-luc) mice (red) exhibits an age-dependent increase, which is indicative of cerebral A β deposition, compared with Tg mice expressing just the Gfap-luc reporter (blue). Intracerebral inoculation of Tg(APP23:Gfap-luc) mice with either A β aggregates purified from the brain of an aged APP23 mouse (black) or A β aggregates formed from synthetic A β (1-40) peptide (green) accelerate the onset of the brain BLI signal increase compared with uninoculated mice, indicating that both inocula contain A β prions. (This figure has been adapted from Stöhr et al. 2012, with permission from the National Academy of Sciences © 2012.)

ed to occur in the brain. Finally, it hinders the development of therapeutics because of the lack of easily and rapidly quantifiable measures of disease. One solution to this problem is the use of bioluminescence imaging (BLI) to monitor the kinetics of A β deposition in living mice. Tg mice that express firefly luciferase (luc) under the control of the glial fibrillary acidic protein (GFAP) promoter (Zhu et al. 2004) emit increased levels of light from their brains in response to stimuli that cause astrocytic gliosis and a concomitant upregulation of GFAP protein in astrocytes. Because GFAP-positive astrocytes are frequently found around the perimeters of A β amyloid deposits in the brain, we hypothesized that Tg(Gfap-luc) mice would be useful for tracking the kinetics of A β deposition in vivo. Indeed, bigenic mice expressing a mutant APP transgene and the Gfap-luc reporter

exhibited age-dependent increases in the brain bioluminescence signal (Fig. 2), providing a quantitative assessment of the kinetics of A β deposition in living mice (Watts et al. 2011).

Two recently described Tg(AD) models have provided significant advances to the field. Knock-in mice in which the mouse APP gene was modified so that it contains a humanized A β sequence and the Swedish and Iberian (I716F) (Guardia-Laguarta et al. 2010) mutations develop typical age-dependent A β pathology and memory deficits (Saito et al. 2014). These mice are noteworthy in that APP is expressed at physiological levels and with correct spatiotemporal patterning. A promising Tg(AD) rat model has also been developed recently. TgF344-AD rats, which express human APP containing the Swedish mutation and a mutant presenilin 1 transgene, develop A β pa-

thology and cognitive deficits and some associated tau pathology and neuronal loss (Cohen et al. 2013).

EVIDENCE FOR THE EXISTENCE OF A β PRIONS IN AD

The pioneering work of Gajdusek, Gibbs, and Alpers revealed that Creutzfeldt–Jakob disease (CJD) and kuru could be transmitted to non-human primates, demonstrating for the first time that these human spongiform encephalopathies are transmissible illnesses (Gajdusek et al. 1966; Gibbs et al. 1968). It is now known that prions composed of misfolded and aggregated prion protein (PrP) are the infectious agent in these diseases (Colby and Prusiner 2011). PrP prions were originally defined as proteinaceous infectious particles that cause rare, transmissible neurodegenerative diseases such as scrapie and CJD (Prusiner 1982) but are now more generally defined as alternative protein conformations that exhibit self-propagation (Prusiner 2012). There are two key features of prions: (1) At least two distinct stable conformational states of the protein exist in the absence of any post-translational modifications, one of which exhibits a propensity for forming multimeric structures and/or aggregates; and (2) the multimeric state is self-propagating, meaning that it can catalyze the conversion of the “normal,” monomeric conformation into an additional copy of the prion conformation.

Evidence that A β becomes a prion during AD pathogenesis is growing. In AD patients, the pattern of A β deposition in the brain is not random in nature. Instead, A β deposition follows a stereotypical progression through five distinct phases. Phases 1–3 are associated with A β deposits occurring in nondemented individuals, whereas phases 3–5 are associated with AD patients (Thal et al. 2002). In phase 1, A β deposits are exclusively found in the neocortex and then spread to the hippocampus in phase 2. In phase 3, A β deposits can additionally be found in the amygdala, thalamus, and striatum. In phase 4, certain areas of the brainstem and the substantia nigra become laden with A β deposits; finally, in phase 5, A β deposits can also

be found in additional brainstem nuclei and the cerebellum. This progressive, nonrandom spreading of cerebral A β deposition is reminiscent of the spread of PrP prions throughout the brain by templated conformational conversion. Unlike in AD, amyloid plaques are only present in the brain in ~10% of CJD cases (DeArmond et al. 2004). However, upon purification, PrP prions aggregate to form rod-like structures that exhibit all of the properties of amyloid, including Congo red birefringence (Prusiner et al. 1983). The molecular and pathological similarities between AD and the PrP prion diseases led to speculation that prions may feature in the pathogenesis of AD, and that like CJD and kuru, AD may be transmissible to nonhuman primates (Prusiner 1984).

Attempts to transmit AD to monkeys produced discordant results (Table 1). Gajdusek and colleagues inoculated 52 different cases of sporadic and familial AD into a variety of primate species and found that only two of the cases transmitted disease (Goudsmit et al. 1980). However, the resultant pathology in the monkeys inoculated with these two cases did not resemble AD; instead, it was identical to that observed in monkeys inoculated with CJD and kuru. Moreover, new preparations of inocula from these two cases failed to transmit disease, suggesting that contamination or other laboratory errors are a more likely explanation for the initial positive transmissions. Similar issues may explain the inability to reproduce an initial finding that buffy coat fractions from the blood of AD patients induce a spongiform encephalopathy in inoculated hamsters (Manuelidis et al. 1988; Godec et al. 1994).

Later, Ridley, Baker, and colleagues showed that marmosets inoculated with brain homogenate from an AD patient develop some A β -containing senile plaques and cerebral amyloid angiopathy 6–7 yr postinjection (Baker et al. 1993, 1994). A total of 24 out of 27 marmosets injected with brain homogenate containing A β aggregates exhibited modest numbers of A β deposits after incubation periods of up to ~8 yr (Ridley et al. 2006). All monkeys that survived >3.5 yr postinoculation exhibited A β deposits. Only five of 29 uninjected mar-

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Table 1. Attempts to transmit Alzheimer's disease to primates

Number of cases inoculated	Host primate(s)	Incubation period examined	Findings	Reference(s)
34 (sporadic AD)	Chimpanzees, capuchins, squirrel monkeys, spider monkeys, African green monkey, stump-tail monkeys	13 cases examined for >50 mo; 21 cases examined for <50 mo	No clinical signs of neurological disease in any of the inoculated animals; A β pathology analysis not performed	Goudsmit et al. 1980
18 (familial AD)	Chimpanzees, capuchins, mangabeys, squirrel monkeys, spider monkeys, African green monkey, stump-tail monkeys, rhesus monkeys, cynomolgus monkeys	4 cases examined for >50 mo; 14 cases examined for <50 mo	16/18 cases produced no clinical signs of neurological disease in the inoculated animals; A β pathology analysis not performed; 2/18 cases produced a spongiform encephalopathy at 23–40 mo postinoculation ^a	Goudsmit et al. 1980
3 (sporadic AD)	Marmosets	Up to 95 mo	No clinical signs of neurological disease in any of the inoculated animals; 8/9 inoculated animals exhibited A β pathology (plaques and cerebral amyloid angiopathy)	Baker et al. 1994; Ridley et al. 2006
1 (familial AD)	Marmosets	Up to 72 mo	No clinical signs of neurological disease in any of the inoculated animals; 4/5 inoculated animals exhibited A β pathology (plaques and cerebral amyloid angiopathy)	Ridley et al. 2006

^aThese two positive transmissions were not reproducible.

mosets aged >10 yr and none of the uninjected marmosets aged 5–10 yr exhibited spontaneous A β deposits. These studies also found that brain homogenate from non-AD patients, synthetic A β aggregates, and CSF from AD patients were poor inducers of A β deposition in marmosets. Importantly, no clinical signs of AD or NFTs were observed in any of the A β -positive inoculated animals, suggesting that although cerebral β -amyloidosis can be initiated or accelerated by inoculation of preformed A β aggregates, the full clinicopathologic spectrum of AD cannot be recapitulated by inoculation, at least within the time frame studied.

USING TRANSGENIC MICE TO STUDY A β PRIONS

The most convincing evidence for the existence of self-propagating A β aggregates (or, simply, A β prions) in AD has been shown by in vivo seeding studies in Tg(AD) mice. In many lines of Tg(AD) mice, such as the widely used Tg2576 and APP23 (Sturchler-Pierrat et al. 1997) models, spontaneous A β deposits are not observed until the animals are older, providing a window during which the induction of A β deposition by inoculation of exogenous A β aggregates can be assessed. In a typical in vivo seeding experiment, young (2- to 3-mo-old) Tg mice (that have not

yet developed deposits) are intracerebrally injected with brain extract containing abundant A β aggregates, and, subsequently, the induction of A β deposition is examined following an incubation period of 3–5 mo. Two inoculation techniques, stereotaxic and non-stereotaxic (“standard”) injections, have been used to introduce exogenous A β aggregates into the brains of Tg(AD) mice. Stereotaxic inoculations commonly involve the injection of 2–3 μ L of brain extract directly into the hippocampus and overlying cortex using a Hamilton syringe. Although this technique is time-consuming, it is advantageous because A β aggregates can be introduced into highly defined brain regions (Eisele et al. 2009). The standard procedure involves the inoculation of $\sim$ 30 μ L of brain extract into the right cerebral hemisphere using a standard syringe and a 27-gauge needle (Stöhr et al. 2012). This technique is less precise (roughly injecting the inoculum into the thalamus and the overlying hippocampal and cortical regions) but is much more rapid.

In 2000, Lary Walker and colleagues showed that intracerebral inoculation of brain extracts from AD patients into Tg2576 mice induced small amounts of cerebral A β deposition following an incubation period of 5 mo (Kane et al. 2000). No A β deposition was observed in mice injected with brain extract from a young individual or in age-matched uninjected animals, and only minor amounts of induced A β deposition were seen in mice inoculated with brain extract from an aged patient without AD. Later, Walker, working with Mathias Jucker and colleagues, revealed that A β aggregates present in the brain extracts were necessary to induce A β deposition (Meyer-Luehmann et al. 2006). Stereotactic inoculation of APP23 mice into the hippocampus and overlying cortex with brain extract from aged Tg(AD) mice resulted in the induction of A β deposition after an incubation period of 4 mo. The induction of cerebral A β deposition could be blocked or significantly attenuated by either (1) immunodepleting the brain extracts of A β aggregates before inoculation, (2) passively immunizing the mice with anti-A β antibodies, or (3) treating the brain extract with formic acid before

inoculation. Depletion of A β aggregates from brain extracts using a small molecule also suppressed seeding activity (Duran-Aniotz et al. 2014). These experiments indicated that, like PrP prions, brain-derived A β aggregates are self-propagating. However, no induced A β deposition was observed in mice inoculated with a variety of synthetic A β aggregate preparations, implying that not all A β aggregates are capable of self-propagation (Meyer-Luehmann et al. 2006).

Although earlier efforts failed to show any seeding of cerebral A β deposition following peripheral or systemic application of A β seeds (Eisele et al. 2009), examining later time points following intraperitoneal inoculation of APP23 mice with Tg(AD) brain extract revealed that cerebral A β deposition can be initiated by peripheral inoculation, suggesting that A β prions, like PrP prions, are neuroinvasive (Eisele et al. 2010). This is not an artifact of ectopic APP expression in the periphery owing to the use of the Thy-1 promoter to drive mutant APP expression in APP23 mice, as cerebral A β deposition can also be induced by peripheral A β inoculation in R1.40 Tg mice, which express mutant APP under the control of its endogenous promoter (Eisele et al. 2014). Similarly, cerebral A β deposition can also be induced by intracerebral inoculation of R1.40 mice with A β -containing brain extract (Hamaguchi et al. 2012), arguing that cerebral A β induction cannot be explained as an artifact arising from improper patterns of APP expression. Although a majority of studies have shown that cerebral A β deposition can be induced in Tg(AD) mice or rats (Rosen et al. 2012) that express mutant APP, it is also possible to induce A β deposition in Tg mice that overexpress wild-type human APP and do not develop spontaneous cerebral A β deposition within their normal lifespan. Intracerebral inoculation of HuAPPwt mice with AD patient brain extract resulted in the induction of A β pathology at $\sim$ 10 mo postinoculation (Morales et al. 2012). It is not yet known whether A β induction can be induced in non-Tg mice or rats.

The specific assemblies of A β responsible for inducing cerebral A β deposition are not cur-

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rently known. A β aggregates purified from the brains of Tg(AD) mice are potent inducers of A β deposition in the brain (Fig. 2) (Stöhr et al. 2012), suggesting that A β aggregates themselves are the infectious prion species. This was confirmed by demonstrating that A β aggregates composed exclusively of synthetic A β peptides can also initiate cerebral A β deposition in APP23 mice (Fig. 2) (Stöhr et al. 2012, 2014). Treatment of A β prion preparations with proteinase K (PK) did not abolish their infectivity (Langer et al. 2011; Stöhr et al. 2012), implying that self-propagating A β aggregates are densely packed and likely large in size. This is supported by the observation that formaldehyde treatment does not inactivate A β prion activity present in brain extracts (Fritschi et al. 2014a) and the remarkable finding that A β prions can persist for up to 6 mo postinoculation in A β -inoculated APP knockout mice (Ye et al. 2015a). However, soluble A β species present in Tg(AD) or AD patient brain extracts that are sensitive to PK digestion can also induce cerebral A β deposition in APP23 mice (Langer et al. 2011; Fritschi et al. 2014b), suggesting that multiple distinct A β prion strains are capable of exhibiting self-propagation.

Like PrP prions, A β prions are capable of inducing cerebral A β deposition even when present at low levels in the inoculum. For example, induced A β deposition was still apparent in Tg2576 mice when injected with 10^5 - to 10^6 -fold dilutions of aged Tg2576 brain extract (Morales et al. 2015). Moreover, brain extracts from patients with mild cognitive impairment or nondemented individuals with AD neuropathology were also capable of inducing cerebral A β deposition in Tg(AD) mice (Duran-Aniotz et al. 2013). Induced A β prions also appear to “spread” away from the original site of inoculation (Eisele et al. 2009; Ye et al. 2015b), providing a potential molecular explanation for the progression of A β pathology observed in AD patients (Thal et al. 2002).

STRAINS OF A β PRIONS

In the PrP prion diseases, distinct strains of prions can be classified according to their incuba-

tion periods upon inoculation into rodents, the resultant clinical signs of disease and neuropathological features, and their biochemical characteristics, such as their relative resistance to protease digestion and their stability upon exposure to chemical denaturants (Collinge and Clarke 2007). A myriad of evidence argues that prion strain-specific properties are encoded within unique conformations of PrP aggregates (Bessen and Marsh 1994; Telling et al. 1996). AD is a clinically and pathologically heterogeneous disorder, with variability present in the age of onset, the rate of cognitive decline, and the morphology and neuroanatomical location of A β pathology (i.e., parenchymal vs. vascular). It is conceivable that some of this heterogeneity may arise because of the presence of distinct strains of A β prions in the brain.

The first evidence for conformational heterogeneity of A β aggregates was observed in A β fibrils generated from synthetic A β using either quiescent or agitated conditions (Petkova et al. 2005). The two types of fibrils exhibited different morphologies when examined using electron microscopy and solid-state nuclear magnetic resonance (NMR) spectroscopy. Moreover, the distinct morphologies were maintained upon serial seeding, indicating that these unique structural states are self-propagating. Variations in the morphology of fibrils formed from synthetic A β have also been obtained by varying the buffer conditions and/or the formation temperature (Meinhardt et al. 2009; Kodali et al. 2010). At the molecular level, structural polymorphism may arise as a result of differences in symmetry and the conformations of A β residues not involved in the core parallel in-register β -sheet structure (Paravastu et al. 2008). Interestingly, A β fibrils formed from synthetic A β can also exhibit strain-like behavior in vivo. Synthetic A β 42 polymerized in the presence of 0.1% (wt/vol) sodium dodecyl sulfate (SDS) resulted in shorter fibrils than when A β 42 was aggregated in the absence of SDS (Stöhr et al. 2014). When inoculated into APP23 mice, A β 42 fibrils generated in the absence of SDS induced a greater number of A β plaques, which contained a higher ratio of A β 42/A β 40 peptides than the plaques in mice

Figure 3. Arctic and Swedish Alzheimer's disease (AD) brain extracts induce distinct pathologies in APP23 mice. (A) Intracerebral inoculation of APP23 mice with brain extract from an AD patient with the Swedish APP mutation, which generates wild-type A β , or brain extract from an AD patient with the Arctic APP mutation, which generates E22G-mutant A β . At 11 mo postinoculation, induced A β cerebral amyloid angiopathy is present in the thalamus (4G8 immunostaining). Whereas mice inoculated with Swedish AD extract exhibited a thin layer of A β deposition surrounding blood vessels (black arrows), many of the blood vessels in mice inoculated with Arctic AD extract were surrounded by thick, "furry" A β deposits (red arrows). (B) Similar morphological differences in A β cerebral amyloid angiopathy were observed at 11 mo postinoculation of APP23 mice with APP23-passaged Swedish and Arctic AD extract, indicating that A β strain-specified properties are serially transmissible. Scale bars, 100 μ m. (This figure has been adapted from Watts et al. 2014, with permission from the National Academy of Sciences © 2014.)

inoculated with A β 42 fibrils produced in the presence of SDS.

Distinct strains (or "morphotypes") of A β prions have also been observed between two different lines of Tg(AD) mice, APP23 and APPPS1 (Radde et al. 2006). Using luminescent conjugated polymers (Sigurdson et al. 2007), it was shown that the A β deposits present in the brains of the two Tg(AD) lines emit distinct fluorescent spectra, which is suggestive of conformationally unique aggregates (Heilbronner et al. 2013). When APP23 A β aggregates were inoculated into APP23 mice, the induced A β prions were spectrally similar to those present in aged APP23 mice. In contrast, when APPPS1 A β prions were inoculated into APP23 mice, the induced A β aggregates produced spectra similar to those present in aged APPPS1 mice, indicating that the brain extracts from aged

APP23 and APPPS1 mice contain distinct strains of self-propagating A β aggregates.

By mixing synthetic A β with fibrils isolated from an AD patient sample, it was shown that the A β aggregates present in AD patients are structurally distinct from those formed spontaneously from synthetic A β (Paravastu et al. 2009). Using a similar approach, it was recently determined that A β aggregates isolated from two different sporadic AD patients produce seeded A β aggregates with unique structural properties, arguing that distinct strains of A β aggregates may exist among AD patients (Lu et al. 2013). Indeed, the A β 42 aggregates in patients with a more rapidly progressive version of AD are conformationally distinct from those in AD patients with a stereotypical disease course, as determined by a conformation-dependent immunoassay (Cohen et al. 2015). The existence

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Table 2. Similarities and differences between PrP and A β prions

Characteristic	PrP prions	A β prions	Reference(s) for A β
Induction of protein aggregation in Tg mice expressing mutant precursor protein	Yes	Yes	Kane et al. 2000; Meyer-Luehmann et al. 2006
Induction of protein aggregation in Tg mice expressing wild-type precursor protein	Yes	Yes	Morales et al. 2012
Induction of protein aggregation in non-Tg mice	Yes	No	Meyer-Luehmann et al. 2006
Induction of protein aggregation in primates	Yes	Yes	Ridley et al. 2006
Induction of a lethal disease in mice	Yes	No	Stöhr et al. 2012
Induction of neuronal loss in mice	Yes	No	Ye et al. 2015b
Induction of astrocytic gliosis in mice	Yes	Yes	Watts et al. 2011
Progressive spreading of protein aggregation	Yes	Yes	
Neuroinvasion following peripheral inoculation	Yes	Yes	Eisele et al. 2014
Horizontal or iatrogenic transmission	Yes	Minimal evidence	Frontzek et al. 2016
Zoonotic transmission	Yes	No	
Serially transmissible	Yes	Yes	Watts et al. 2014
Existence of distinct strains	Yes	Yes	Stöhr et al. 2014
Titratable levels of infectivity	Yes	Yes	Morales et al. 2015
Resistance to digestion with proteinase K	Yes	Yes	Stöhr et al. 2012
Resistance to formaldehyde inactivation	Yes	Yes	Fritschi et al. 2014a
Adherence to stainless steel wires	Yes	Yes	Eisele et al. 2009

of distinct A β strains among AD patients has also been demonstrated using brain extracts from two patients with early-onset familial versions of the disease. Using a conformational stability assay that measures the relative resistance of A β aggregates to chemical denaturation, it was shown that the A β aggregates from an AD patient with the Swedish mutation in APP can be distinguished from those in an AD patient with the Arctic mutation (E693G) (Nilsberth et al. 2001) in APP (Watts et al. 2014). When brain extracts from these two patients were inoculated into APP23 mice, distinct vascular A β pathologies were observed (Fig. 3), and these differences were maintained upon second passage in APP23 mice. These results reveal that, like PrP prions, strain-specific properties of A β prions are serially transmissible in mice.

CONCLUDING REMARKS

It is becoming increasingly clear that A β prions exhibit many similarities to prions composed of PrP (Table 2), making it more difficult to refute the notion that A β can become a prion during AD. However, there is currently minimal evi-

dence to suggest that A β prions can be transmitted from human to human. Many individuals that received human cadaveric growth hormone injections ultimately died of CJD because the pituitary extracts were contaminated with PrP prions (Brown et al. 2000). Although no increased incidence of AD has been observed in living individuals who received growth hormone injections (Irwin et al. 2013), it has recently been shown that the brains of growth hormone recipients who died of CJD contain much higher levels of A β deposition than would be expected (Jaunmuktane et al. 2015). One possible interpretation is that A β prions were present in the growth hormone extracts, which initiated cerebral A β deposition following peripheral injection. Increased amounts of A β deposition have also been observed in patients that developed iatrogenic CJD following dura mater grafts (Frontzek et al. 2016). Notably, tau deposition was not observed in either of these instances, potentially indicating an early stage of AD pathogenesis. Although iatrogenic AD transmission is only one potential explanation for these observations, sterilization methods for surgical tools may need to be reconsid-

ered, especially because A β prions remain active once bound to stainless steel (Eisele et al. 2009).

Although AD is unlikely to be transmissible among people under physiological circumstances, the realization that A β peptides can become prions during disease has many potential implications. First, the existence of self-propagating A β prions may provide a molecular explanation for why AD is a progressive disorder. Spreading of A β prions along neuroanatomical pathways in conjunction with a potential stimulation of tau prion formation may cause a progressive worsening of disease symptoms. Moreover, like CJD, ~90% of AD cases are sporadic, suggesting that the initiating event may be the rare, age-related stochastic formation of a self-propagating A β aggregate seed. In early-onset familial AD, the necessity for A β prion formation may explain why disease most commonly manifests in the fifth or sixth decade of life, despite the fact that elevated levels of pathogenic A β are produced from birth. Second, the formation of self-propagating A β species may represent an early event in disease progression that can be targeted pharmacologically. Third, the existence of distinct strains of A β prions poses a considerable challenge for the development of A β -directed therapeutics for AD. Heterogeneity in the conformation of A β aggregates may partially explain the disappointing results obtained thus far in clinical trials of A β monoclonal antibodies (Delrieu et al. 2012) because antibody efficacy may be highly strain specific. Although studies of the biology of A β prions are still in their infancy, they hold great promise for understanding basic disease mechanisms and for the development of effective therapeutics for AD.

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