The Prion-Like Properties of Amyloid- β Assemblies: Implications for Alzheimer's Disease

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Since the discovery that prion diseases can be transmitted to experimental animals by inoculation with afflicted brain matter, researchers have speculated that the brains of patients suffering from other neurodegenerative diseases might also harbor causative agents with transmissible properties. Foremost among these disorders is Alzheimer's disease (AD), the most common cause of dementia in the elderly. A growing body of research supports the concept that the pathogenesis of AD is initiated and sustained by the endogenous, seeded misfolding and aggregation of the protein fragment amyloid- β (A β). At the molecular level, this mechanism of nucleated protein self-assembly is virtually identical to that of prions consisting of the prion protein (PrP). The formation, propagation, and spread of A β seeds within the brain can thus be considered a fundamental feature of AD pathogenesis.

Alzheimer's disease (AD) is the most frequent cause of dementia and a growing social, medical, and economic challenge to societies in which the elderly population is rapidly growing (Dartigues 2009; Holtzman et al. 2011; Reitz et al. 2011). The involvement of abnormal proteins in AD has been evident since Alois Alzheimer's original histopathological descriptions of the disease in the early 20th century (Alzheimer 1906). Even today, a conclusive diagnosis of AD in a patient with dementia requires the significant presence of two cardinal brain lesions at autopsy: amyloid- β (A β) plaques and neurofibrillary tangles (NFTs) (Fig. 1). The de-

fining components of plaques are extracellular collections of aggregated A β protein, whereas NFTs consist of intracellular bundles of hyperphosphorylated tau protein (Duyckaerts et al. 2009; Holtzman et al. 2011). In both cases, the proteins that accumulate assume a tertiary structure (or fold) that is unusually rich in β -sheet, which in turn promotes the structural corruption and self-assembly of like molecules into small oligomeric and larger fibrillar assemblies with neurotoxic properties (Haass and Selkoe 2007; Klein 2013). The resulting aggregates have features that are often characteristic of amyloid (Eisenberg and Jucker 2012). Although

Editor: Stanley B. Prusiner

Additional Perspectives on Prion Diseases available at www.perspectivesinmedicine.org

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Advanced Online Article. Cite this article as *Cold Spring Harb Perspect Med* doi: 10.1101/cshperspect.a024398

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Figure 1. The canonical histopathology of Alzheimer's disease (AD). Amyloid- β ($A\beta$) plaques consist of extracellular deposits of $A\beta$ (brown; detected by immunostaining with a polyclonal antibody to $A\beta$), and neurofibrillary tangles (NFTs) consist of intracellular masses of ectopic tau protein (purple; detected by immunostaining with a monoclonal antibody to tau). Scale bar, 100 μ m.

the presence of amyloid signifies a proteopathic process, amyloid per se is not always required for the complete manifestation of disease. Both $A\beta$ plaques (Fig. 2) and tau lesions can be modeled in transgenic mice (Jucker 2010). With the progression of AD, $A\beta$ deposition and NFTs increase in number and affect large areas of the brain in a characteristic and brain region–

specific manner (Braak and Braak 1991; Thal et al. 2002; Jucker and Walker 2013). In addition to these pathological hallmarks and diagnostic lesions, the AD brain is typified by impaired synaptic function, neuroinflammation, and neuronal loss, which ultimately contribute to the full expression of dementia (Holtzman et al. 2011; Nelson et al. 2012).

Figure 2. Similar appearance of amyloid- β ($A\beta$) deposits in the brain of an Alzheimer's disease (AD) patient and an $A\beta$ -precursor protein (APP)-transgenic mouse model. (A) $A\beta$ deposits in the neocortex of an AD patient. (B) $A\beta$ deposits in the neocortex of an APP23 transgenic mouse. An anti- $A\beta$ specific polyclonal antibody (black) was used for immunostaining. Sections were counterstained with Congo red, a generic stain for amyloid. Scale bar, 200 μ m.

In addition to plaques, A β accumulates to a variable extent in the walls of cerebral blood vessels in AD patients; this cerebral amyloid angiopathy (CAA) of the A β -type, although not pathognomonic for AD, is a risk factor for hemorrhagic stroke (Yamada 2013) and can independently contribute to cognitive decline (Biffi and Greenberg 2011; Reijmer et al. 2015). Moreover, in most cases of AD (particularly in older patients), typical pathological features are accompanied by variable amounts of comorbid lesions, such as vascular abnormalities and/or aggregates of other, non-AD-specific pathogenic proteins such as α -synuclein, TDP-43, and others (Neuropathology Group, Medical Research Council Cognitive Function and Aging Study 2001; Knopman et al. 2003; Schneider et al. 2007; Nelson et al. 2012).

THE PRIMACY OF A β IN THE AD PATHOGENIC CASCADE

Although the degree of tauopathy correlates more strongly with cognitive decline than does the buildup of A β (Giannakopoulos et al. 2003), extant evidence indicates that in AD (Hardy and Selkoe 2002; Holtzman et al. 2011; Nelson et al. 2012) and in genetically modified mice (Götz et al. 2001; Lewis et al. 2001; Bolmont et al. 2007; Héraud et al. 2014; Stancu et al. 2014; Vasconcelos et al. 2016), tauopathy is downstream from A β proteopathy. Moreover, the genetic causes of autosomal dominant AD identified so far all affect A β by enhancing its release from the A β -precursor protein (APP) or its tendency to self-aggregate (Hardy and Selkoe 2002). In contrast, a rare mutation in the APP gene that causes an amino acid substitution at position 2 of A β (A673T according to APP770 numbering) reduces the production of A β following β -secretase cleavage (Jonsson et al. 2012) and also lowers the propensity of A β to aggregate (Benilova et al. 2014); the A673T mutation thereby also lessens the risk of developing AD (Jonsson et al. 2012). Substitution of valine for alanine at this site (A673V) *enhances* the production and aggregation of A β and causes an autosomal recessive form of AD (Di Fede et al. 2009). Furthermore, assessment of biomarkers in subjects with

autosomal dominant causative mutations and in subjects with idiopathic AD before the likely age of dementia onset shows that A β changes in the brain are the first harbinger of impending disease, and that this can occur decades before clinical dementia sets in (Jack et al. 2010; Holtzman et al. 2011; Selkoe 2011; Bateman et al. 2012). These findings together highlight the pivotal role of A β in the pathogenesis of AD.

EXPERIMENTAL EVIDENCE FOR THE PRION-LIKE SEEDING OF A β AGGREGATION

Since the discovery that prion diseases can be transmitted to experimental animals by inoculation with afflicted brain fractions, researchers have speculated that the brains of patients suffering from other neurodegenerative diseases might also harbor causative agents with transmissible properties (Prusiner 1984; Gajdusek 1994). A team in Great Britain reported that A β load is increased in the brains of nonhuman primates by the intracerebral injection of AD brain homogenates (Baker et al. 1993). However, the experiments required an incubation period of >5 yr, and the causative agent and mechanism of action remained uncertain. In the late 1990s, as the first transgenic mouse models of cerebral β -amyloidosis became available (Games et al. 1995; Hsiao et al. 1996; Sturchler-Pierrat et al. 1997), we set out to definitively test the hypothesis that the prion paradigm of nucleated protein self-assembly also applies to A β . This series of studies, in conjunction with investigations in other laboratories, now provides support for the concept that the molecular properties of pathogenic A β assemblies are virtually identical to those of prion protein (PrP) prions (Walker and Jucker 2015).

In our first experiments, extracts of autopsy-derived brain samples from AD patients and controls were injected stereotactically into the hippocampal formation and/or neocortex of young, predepositing APP-transgenic mice (Kane et al. 2000; Walker et al. 2002; Meyer-Luehmann et al. 2006). After incubation periods ranging from a few hours to 12 mo, the brains were analyzed immunohistochemically. Because only small amounts of extract were injected

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(typically 1–2.5 μL , containing ~ 10 ng $\text{A}\beta/\mu\text{L}$), little or no immunohistochemically detectable $\text{A}\beta$ remained after a few days or more of incubation. However, by 3 to 5 mo postsurgery, at a point when the transgenic mice had not yet begun to form endogenous $\text{A}\beta$ plaques and CAA, $\text{A}\beta$ deposits emerged and increased dramatically with longer incubation intervals (Fig. 3).

The degree of $\text{A}\beta$ -seeding in mice is directly proportional to the concentration of the brain

extract (Meyer-Luehmann et al. 2006; Fritsch et al. 2014b). Seeded $\text{A}\beta$ deposits are both diffuse and congophilic, and dense-core (congophilic) plaques are associated with cellular reactivity that includes microgliosis, astrogliosis, and abnormal neurites containing increased APP and hyperphosphorylated tau. Importantly, no $\text{A}\beta$ deposits emerged in nontransgenic host mice, and brain extracts from non-AD control donors that lacked $\text{A}\beta$ deposition did not induce signif-

Figure 3. Induction and spread of amyloid- β ($\text{A}\beta$) lesions in an $\text{A}\beta$ -precursor protein (APP)-transgenic mouse model. $\text{A}\beta$ seed-laden brain extract was bilaterally injected into the hippocampus and overlying neocortex of R1.40 APP-transgenic mice. The injection site is marked in purple. (A) After a 6-mo incubation period, $\text{A}\beta$ deposition appeared mainly in the hippocampus. (B) After a 12-mo incubation period, spreading of $\text{A}\beta$ deposition to neighboring brain regions and throughout much of the forebrain was observed. (From Fritsch et al. 2013; modified with the authors' permission.)

icant A β lesions (Kane et al. 2000; Meyer-Luehmann et al. 2006). NFTs per se have not been detected in seeded APP-transgenic mouse models and would likely require the expression of human-sequence tau in host mice (Bolmont et al. 2007).

These findings indicate that A β seeding requires both a donor brain extract that contains A β seeds and a host that is capable of generating A β plaques and/or CAA of the A β type. Because injections of control brain extracts failed to seed plaque formation, these findings also mitigate against the possibility that the induction of A β deposition is simply caused by brain injury. The concern that the seeding effect might result from factors in the human brain that indirectly stimulate A β aggregation, such as a human-specific virus or an immune response to the foreign brain fractions, was ruled out by a robust seeding response to A β -rich brain extracts from aged APP transgenic donor mice of the same strain as the host mice (Meyer-Luehmann et al. 2006; Watts et al. 2011).

The next step was to define the nature of the A β seeds. Denaturation of brain extracts with formic acid (Meyer-Luehmann et al. 2006), or the specific depletion of A β by antibodies or reagents that bind and remove amyloid proteins from the extract, abrogated the seeding effect (Meyer-Luehmann et al. 2006; Duran-Aniotz et al. 2014). Seeding was also blocked when the extract was mixed with an A β antibody and then injected into the brain (Meyer-Luehmann et al. 2006).

These results confirmed that A β is essential to the seeding capacity of brain extracts, but they left open the question of whether pure, aggregated, synthetic A β is able to induce deposition in mice. In early experiments, the injection of various amounts of synthetic A β fibrils did not cause obvious induction of new plaques up to 5 mo postinjection (Meyer-Luehmann et al. 2006). This finding was not entirely unexpected, given the poor potency of recombinant PrP in inducing brain disease (Legname et al. 2004). More recently, however, it was shown that with a larger dose of aggregated A β and a longer incubation time, A β deposition can be instigated by multimeric, synthetic A β (Stöhr et al. 2012).

A β seeds, then, like PrP prions, gain considerable potency when formed within the brain. The seeded conversion of synthetic A β into potent, in vivo-active A β seeds has recently been achieved in a hippocampal slice culture model (Novotny et al. 2016). Further deciphering of the factors responsible for the conversion will be important to understanding the pathogenicity of multimeric A β in AD. For instance, the addition of certain cofactors to the medium in which synthetic PrP is aggregated augments the seeding potential of synthetic PrP prions (Wang et al. 2010; Deleault et al. 2012; Zhang et al. 2014). It will be informative to determine whether cofactors might also increase the potency of synthetic A β seeds.

THE INTERACTION OF A β STRAINS AND HOST FACTORS

To induce A β deposition in the in vivo seeding model, it is necessary for the host animal to express seeding-capable A β (Kane et al. 2000; Meyer-Luehmann et al. 2006; Morales et al. 2012; Rosen et al. 2012). In earlier studies, transgenic mouse models that eventually develop endogenous A β lesions as they age were used. Prion disease, however, is induced de novo by infection with PrP prions in animals that otherwise would never have manifested the disease. To determine whether A β deposits can also be generated de novo in relatively resistant animals, A β -seeding experiments were undertaken in APP-transgenic mice (Morales et al. 2012) and rats (Rosen et al. 2012) that do not generate plaques or CAA within their normal life spans. In both instances, A β deposition was induced in the brain after a suitable incubation period.

The existence of variant structural strains of A β is increasingly well established (Eisenberg and Jucker 2012; Lu et al. 2013; Hatami et al. 2014; Spirig et al. 2014; Cohen et al. 2015). Growing evidence supports the hypothesis that A β seeds, like PrP prions (Aguzzi et al. 2007; Collinge and Clarke 2007; Prusiner 2013), can also adopt different molecular conformations that are linked to their functionality in vivo (Meyer-Luehmann et al. 2006; Eisenberg and Jucker 2012; Stöhr et al. 2014; Watts et al. 2014).

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APP-transgenic mice (APP23 mice) and transgenic mice expressing human APP along with human presenilin-1 (APPPS1 mice) develop parenchymal A β deposits that differ morphologically at the light-microscopic level (Heilbronner et al. 2013). When A β -laden brain extract from one model was injected intracerebrally into the other model, the lesion morphologies, as revealed by immunohistochemistry, and the molecular architecture of the deposited A β , as assessed by amyloid conformation-sensitive oligothiophene dyes, showed characteristics of both the host and seeding extract (Heilbronner et al. 2013). Interestingly, the ratio of A β 40 to A β 42 in the induced A β deposits in host mice also was influenced by exogenous seeds, suggesting that this ratio may contribute to the strain-like properties of A β assemblies (Heilbronner et al. 2013). Transmission studies have found that brain extracts from AD patients carrying either the Swedish or Arctic mutation injected into the brains of susceptible mice induced distinct A β pathologies that could be serially propagated and maintained after multiple passages (Watts et al. 2014). Finally, in a given host model, if seeds are infused into brain regions other than the hippocampus, the deposits that emerge are often typical of the morphotypes displayed by the endogenous (unseeded) lesions that form in the respective structures as the mice age (Eisele et al. 2009). Hence, not only the host mouse but also the local brain conditions influence the types of lesions that are induced by exogenous A β seeds.

THE SIZE AND POTENCY OF A β SEEDS

Prions exist in a range of sizes, and the most potent PrP prions appear to be small, soluble species (Silveira et al. 2005). To assess the size range of A β seeds, brain extracts were subjected to ultracentrifugation ($100,000\times g$ for 1 h). Most (>99%) of the A β from the extract sedimented in the pellet, which, when injected intracerebrally into mice, seeds A β aggregation almost as effectively as does the original brain extract. Surprisingly, however, soluble A β in the high-speed supernatant seeded $\sim 30\%$ as much histochemically detectable A β deposition as did the insoluble pellet, although <1% of the

A β was in the soluble fraction. Therefore, small, soluble A β assemblies, like small PrP prions, are highly effective seeds. Given their limited dimensions, it is conceivable that soluble A β seeds traffic through the brain more readily than do larger fibrils. Interestingly, these soluble seeds, unlike insoluble multimers, are quite sensitive to destruction by proteinase K (PK), suggesting that they may be particularly susceptible to therapeutic intervention (Langer et al. 2011).

To assess the potency of A β seeds in stimulating cerebral A β -deposition, serially diluted brain extracts from autopsied AD patients were injected into the hippocampus of young, APP-transgenic host mice. The degree of induction diminished with increasing dilution, but even subattomolar levels of brain-derived A β were found to stimulate A β -proteopathy in the hosts (Fritsch et al. 2014b). In a recent experiment, A β seed-rich brain extracts were injected into APP-null host mice that, because of the absence of A β , are incapable of replicating A β seeds; 6 mo later, brain extracts from these APP-null mice were still able to seed A β deposition in APP-transgenic hosts, indicative of extraordinary potency and robustness of A β seeds (Ye et al. 2015a). Surprisingly, A β in the cerebrospinal fluid (CSF) of AD patients and aged APP-transgenic donor mice was devoid of significant *in vivo* seeding activity, even at levels of A β exceeding those in the most concentrated brain extracts (Fritsch et al. 2014b). The reasons for the inability of A β in the CSF to seed *in vivo* remain uncertain, but the mechanism could reveal a novel means of impeding the seeding cascade in the brain.

THE ROBUSTNESS OF A β SEEDS

Although PrP prions vary in their stability (Tzaban et al. 2002; Choi et al. 2010; Zou et al. 2010; Gambetti et al. 2011), a notable characteristic of infectious prions is that some of them are quite durable, even under harsh environmental conditions (Appel et al. 2001; Wiggins 2009). The ability of these prions to retain their pathogenic properties contributes to their infectivity, including rare instances of infection in neurosurgical patients exposed to PrP

prion-contaminated surgical instruments that had been sterilized via conventional methods (Brown et al. 2012; Thomas et al. 2013). Studies in experimental animals confirm the persistent infectivity of PrP prions bound to stainless-steel wire (Flechsigs et al. 2001), even after the wire has been exposed to formaldehyde (Zobeley et al. 1999).

A first hint that A β seeds are also durable agents came from studies in which A β -rich brain extract was boiled for 5 min and still retained its seeding capacity (Meyer-Luehmann et al. 2006). In later studies drawing from work in the PrP prion field, a minute quantity of A β -rich brain extract was dried onto stainless-steel wires, and the wires were implanted in the brains of APP-transgenic host mice (Eisele et al. 2009). After an incubation period of 4 mo, A β lesions were induced in the region immediately surrounding the wire and, to a lesser extent, in more distant areas. Plasma sterilization of the contaminated wires before implantation prevented plaque induction, but heating them for 10 min at 95°C did not (Eisele et al. 2009). Although this study suggests that A β seeds on insufficiently sterilized surgical instruments might increase the risk of AD, presently this is only a theoretical possibility.

One of the first clues that the agent that transmits PrP prion disease is highly unorthodox surfaced unexpectedly in the 1930s when William Gordon immunized sheep against a viral illness called louping-ill (Gordon 1946). The vaccine was prepared from formaldehyde-fixed nervous tissue derived from sheep that had been sick with louping-ill. Although the vaccine worked well to reduce the incidence of louping-ill, after several years the vaccinated sheep began to develop scrapie. Gordon surmised that some of the sheep used to prepare the vaccine were also incubating the scrapie agent and that the agent is resistant to inactivation by formaldehyde (Gordon 1946). This conclusion has been supported by subsequent research (Pattison 1965; Brown et al. 1990).

To determine whether A β seeds are similarly resistant to formaldehyde inactivation, formaldehyde-fixed brain samples from AD patients and APP-transgenic mice were injected into

APP-transgenic hosts. The fixed brain samples retained their seeding potential, even after as long as 2 yr in formaldehyde (Fritsch et al. 2014a). Additionally, the spectral patterns of luminescent conjugated oligothiophenes bound to A β indicated that the molecular architecture of the A β seeds was maintained in fixed tissue and could be faithfully transmitted to the host mice (Fritsch et al. 2014a).

TRAFFICKING OF A β SEEDS

Trafficking within the Brain

PrP prion-laden extracts injected into the brains of transgenic mice yield pathology that is not restricted to the injection site; rather, the PrP prions propagate and spread throughout most of the brain (Fraser 1982; Buyukmihci et al. 1983; Kimberlin and Walker 1986; Liberski et al. 2012; Rangel et al. 2014). In the case of AD, the neuroanatomical distribution of plaques and tangles at different disease stages suggests that the lesions propagate among axonally connected brain areas (Saper et al. 1987; Arnold et al. 1991; Braak and Braak 1995), a possibility that is garnering support from contemporary imaging modalities (Bero et al. 2011; Zhou et al. 2012; Iturria-Medina et al. 2014; Raj et al. 2015). Experimentally, within 24 h of injecting A β -rich brain extract into the hippocampus, immunohistochemical examination shows that the extract diffuses away from the injection site and tends to concentrate along the hippocampal fissure, around blood vessels, and in the subpial zone, regions that exhibit a strong seeding response following a much longer incubation period (Walker et al. 2002; Ye et al. 2015b). The injected A β rapidly becomes undetectable histochemically, and a lag period ensues before the focal emergence of induced deposits in the injected hippocampus, usually after a month or more depending on the mouse model (Kane et al. 2000; Meyer-Luehmann et al. 2006; Eisele et al. 2014). Over time, A β deposits then begin to appear in other brain regions, most notably in the entorhinal cortex ventrolateral to the dorsal hippocampal injection site (Walker et al. 2002; Meyer-Luehmann et al. 2006; Eisele et al. 2009).

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When the seeds are placed in the entorhinal cortex, the earliest secondary deposits emerge selectively in the hippocampal formation (Eisele et al. 2009). Because the entorhinal cortex is a major source of neocortical communication with the hippocampal formation (Suh et al. 2011; Arszovszki et al. 2014), these studies provided the first clues that neuronal pathways might define the spread of A β pathology through the brain.

To further test the hypothesis that A β seeds propagate by sequential seeding requires extending the incubation period into the age when most transgenic mouse models begin to generate deposits on their own. For this purpose, the R1.40 APP-transgenic mouse model (Lamb et al. 1997) was used. These mice do not start to form endogenous A β plaques until 15 mo of age, providing a wide time window within which to observe the spread of lesions following focal seeding in the hippocampus. R1.40 mice were injected intracerebrally with A β seeds at 3 mo of age, and by 15 mo, much of the brain was beset by A β deposits (Hama-guchi et al. 2012). Analysis of seeded R1.40 mice and APPS1 mice at different time points supports the hypothesis that the infusion of exogenous seeds into the hippocampus elicits the spread of lesions along axonal routes; specifically, A β deposits appear in structures of the limbic connectome and subsequently in regions that are increasingly distant from the initial site of injection (Fig. 3) (Ye et al. 2015b). A similar systematic emergence of endogenous A β lesions has been reported in an APP-transgenic mouse model expressing Arctic mutant A β (Rönnbäck et al. 2012).

These findings suggest that A β aggregates traffic along neuronal pathways, but whether this occurs by constrained diffusion along fiber pathways or by active uptake and transport by neurons has not yet been determined in vivo. In addition, the role of the transgene promoter in defining the regional emergence of lesions remains to be fully defined. However, in vitro studies have shown that cultured neurons can take up and transport multimeric A β (Nath et al. 2012; Domert et al. 2014; Song et al. 2014). In addition, it is important to consider the possibility

that exogenous A β seeds (and their endogenous descendants) can translocate by other means. In mice seeded intrahippocampally with A β -rich brain extracts, we have noted the premature appearance of CAA in the thalamus (Meyer-Luehmann et al. 2006). How thalamic CAA is stimulated in hippocampally seeded mice remains unknown. In this light, alternative modes of seed trafficking, beyond passive diffusion and neuronal transport, should be considered. These include perivascular and paravascular flow (Weller et al. 1998; Thal et al. 2007; Iliff et al. 2012) or uptake and transport by nonneuronal cells such as macrophages (Eisele et al. 2009) (see below).

Trafficking from the Periphery to the Brain

The infectivity of PrP seeds commonly involves their translocation from the periphery to the brain (Aguzzi 2003). To study whether A β seeds delivered to peripheral sites can stimulate the formation of A β plaques or CAA in the brain, APP transgenic mice were inoculated via various routes. In a first report, the oral, intranasal, and intravenous delivery of A β seeds failed to induce significant plaque formation in the brain, at least within the incubation period examined (Eisele et al. 2009). However, in subsequent studies using a slightly prolonged incubation time, the injection of aggregated A β -rich brain extracts into the peritoneal cavity induced significant cerebral A β -amyloidosis, particularly in the cerebral vasculature (Eisele et al. 2010, 2014). The magnitude of the seeding effect correlated with the amount of intraperitoneally inoculated A β seeds and with the expression of APP/A β in the brain (but not in the periphery). The pattern of immunoreactive lesions in this model suggests that the A β seeds enter the brain at multiple sites (Eisele et al. 2014). Thus, A β seeds, like PrP prions, can reach the brain from outside the central nervous system (CNS). How they do this remains uncertain; transport by macrophages through the bloodstream is one possibility (Eisele et al. 2014; Cintron et al. 2015), but alternative routes of conveyance (such as neuronal transport) could also be involved.

EVIDENCE FOR THE PRION-LIKE SEEDING OF A β IN HUMANS

From the late 1950s until 1985, a number of children with conditions such as short stature were treated with growth hormone that had been isolated from cadaveric human pituitary glands. Much later it was discovered that some batches of the hormone were contaminated with PrP prions, resulting in iatrogenic Creutzfeldt–Jakob disease (CJD) in a subset of patients (Rudge et al. 2015). Recently, eight hormone recipients in Great Britain who died of CJD at ages ranging from 36 to 51 yr were examined for the co-presence of AD-type lesions. Four of them had significant A β accumulation in the form of A β plaques and CAA, and two others had sparse A β deposits (Jaunmuktane et al. 2015). These findings raise the possibility that some batches of growth hormone were contaminated with A β seeds that originated from pituitary glands collected from patients who had died with AD (or incipient AD) (Jucker and Walker 2015). Because the growth hormone recipients had died of CJD, it is unknown whether they ultimately would have developed AD (none of them displayed signs of tauopathy). It will be informative to follow the surviving recipients who did not manifest CJD to assess their relative risk of AD and other neurodegenerative proteopathies. A preliminary analysis in the United States suggests that growth hormone recipients may not be more likely to develop AD (Irwin et al. 2013), although a very long incubation period is likely. Also important will be to examine any remaining batches of cadaveric growth hormone for the presence of A β and other types of prion-like seeds. Very recently, CJD patients who had received PrP prion-contaminated dura mater transplants many years earlier were also found to have significantly increased A β plaques and CAA (Frontzek et al. 2016).

These studies have furnished the first evidence that the aggregation of a protein other than PrP can be instigated in the human brain by exogenous seeds, but in neither case was full-blown AD induced, nor do the findings

suggest that AD can be transmitted from person to person under ordinary circumstances. Rather, current evidence indicates that AD begins endogenously with the misfolding, corruptive templating, and self-assembly of A β (Jucker and Walker 2013). As noted above, the risk of AD is increased by mutations and polymorphisms that promote A β misfolding and aggregation. Whether and how physiological and environmental factors influence the A β cascade and how the aggregation of A β is ultimately linked to dementia remain open questions, but it now seems likely that A β aggregation is a central mechanism on which risk factors converge to facilitate the development of AD.

CONCLUSIONS: THE PRION PARADIGM, A β , AND AD

Considerable research now supports the conclusion that A β can be induced to aggregate and spread in the brain by a prion-like mechanism. AD involves a clinically silent period of intracellular protein aggregation that precedes dementia by decades (Jack et al. 2010; Holtzman et al. 2011; Selkoe 2011; Bateman et al. 2012). In this light, the seeding model of A β deposition substantiates a primary role for A β aggregation in the early stages of AD and reinforces the logic of therapeutically targeting A β seeds (Jucker and Walker 2011), preferably early in the pathogenic cascade.

In Table 1, we summarize the features of A β seeds that justify their inclusion within the widening context of the prion concept. Fully developed AD has not yet been induced in any animal model; indeed, AD appears to be unique to humans (Walker and Cork 1999; Jucker 2010; Heuer et al. 2012). In addition, there is no definitive evidence to date that AD per se can be transmitted to humans by infection with exogenous A β seeds. However, the exogenous seeding model provides compelling evidence for a molecular mechanism by which A β seeds act to instigate and perpetuate AD pathology. Present knowledge favors a pathogenic model in which AD originates from the endogenous generation of A β seeds. For these reasons, and because

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Table 1. Comparison of PrP prions and A β seeds

Properties	PrP prions	A β seeds
Structure		
β -sheet-enriched conformation	Yes	Yes
Aggregation	Yes	Yes
Seeding capacity		
Seeds initiate pathology	Yes	Yes
Purified and synthetic materials seed	Yes	Yes
Seeds instigate de novo deposition	Yes	Yes
Strain variation		
Existence of different strains	Yes	Yes
Stability		
Differential resistance to PK digestion	Yes	Yes
Resistance to high temperature	Yes	Yes
Resistance to formaldehyde fixation	Yes	Yes
Trafficking		
Spreading within and to the brain	Yes	Yes
Infectivity		
Serial transmissibility in mice	Yes	Yes
Transmissibility to humans	Yes	(Yes) ^a

PK, Proteinase K.

^aProbable transmission of A β deposition.

the term “prion” is now widely used to refer to proteinaceous agents of biological information transfer in both health and disease, we suggest that the power of the prion concept can be enhanced by defining prions as “proteinaceous nucleating particles” (Walker and Jucker 2015). In light of this more comprehensive definition, research now supports the designation of A β seeds as A β prions. Defining prions according to their molecular properties has the additional advantage of mitigating unwarranted concern about the transmissibility of noninfectious proteopathies.

ACKNOWLEDGMENTS

We thank Sarah Fritschi and Ulrike Obermüller for their help in preparing this review and Simone Eberle for editorial assistance.

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