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Aβ seeds and prions: How close the fit?

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ABSTRACT. The prion paradigm is increasingly invoked to explain the molecular pathogenesis of neurodegenerative diseases involving the misfolding and aggregation of proteins other than the prion protein (PrP). Extensive evidence from \textit{in vitro} and \textit{in vivo} studies indicates that misfolded and aggregated Aβ peptide, which is the probable molecular trigger for Alzheimer’s disease, manifests all of the key characteristics of canonical mammalian prions. These features include a β-sheet rich architecture, tendency to polymerize into amyloid, templated corruption of like protein molecules, ability to form structurally and functionally variant strains, systematic spread by neuronal transport, and resistance to inactivation by heat and formaldehyde. In addition to Aβ, a growing body of research supports the view that the prion-like molecular transformation of specific proteins drives the onset and course of a remarkable variety of clinicopathologically diverse diseases. As such, the expanded prion paradigm could conceptually unify fundamental and translational investigations of these disorders.

KEYWORDS. Aβ, Alzheimer, amyloid, aging, dementia, neurodegeneration, prion, proteopathy, seeding, tau
Since the initial clinicopathologic characterization of Kuru and the discovery that human spongiform encephalopathies are transmissible, researchers have hypothesized that these extraordinary maladies might share etiologic features with other neurodegenerative diseases such as Alzheimer’s disease (AD) and Parkinson’s disease.1,2 A key mechanistic commonality is the pathologic accumulation of specific misshapen proteins within the brain.3 In the prion diseases, this process can be initiated by infection, i.e., the invasion of the body by exogenous seeds of misfolded, aggregated prion protein (PrPSc), which proliferate by the templated corruption of naïve PrP molecules and ultimately impair brain function. However, most human prion diseases are not instigated by infection, but rather begin with the endogenous generation of PrPSc, which then multiplies by the same molecular mechanism as that induced by exogenous PrP-prions.4

Emerging data support the hypothesis that other neurodegenerative disorders similarly involve the endogenous misfolding, aggregation, and systematic spread of disease-specific proteins within the brain, reminiscent of PrP-prions.3,5,6 Unlike PrP-prions, however, these diseases are not infectious in the sense of transmissibility from one person to another under ordinary conditions.3,7 Hence, despite important molecular similarities, the fact that prions are defined as infectious agents has generated debate in the scientific community as to whether the term ‘prion’ should be expanded to include pathogenic proteins that are not infectious by conventional definitions.3

One of the proteins in question is the Aβ peptide, an amyloidogenic cleavage product of the Aβ-precursor protein (APP) that misfolds and aggregates in the brains of patients with AD.8 The accumulation of aberrant Aβ appears to be the earliest critical event in the AD pathogenic cascade;9 this is closely followed by the multimerization of misfolded tau protein, which constitutes neurofibrillary tangles and contributes strongly to cognitive dysfunction.10 These two proteins thus have been the focus of therapeutic efforts to modify the course of AD, with most of the effort to date concentrated on the putative prime mover, Aβ.8 The extent to which Aβ seeds resemble PrP-prions has important implications for the strategic consolidation of research efforts in fields that heretofore have been largely separate. In this commentary, we address the broader question of whether the term ‘prion’ is appropriate for Aβ given the current scientific evidence, and what additional experiments are necessary for incorporating Aβ (and other pathogenic proteins) into the prion paradigm. While studies of prion-like proteins in yeast and other organisms have yielded many important insights into prion biology,11-13 we confine our present discussion to disease-associated proteins in mammals.

**COMPARING Aβ SEEDS TO PRP-PRIONS**

The defining property of prions is the self-propagation of alternatively folded protein conformations by the templated corruption of like proteins.5 By this molecular definition alone, the seeds of Aβ and many other proteins can be defined as prions. However, other traits have been invoked to characterize infectious PrP-prions, including the tendency to form amyloid, folding into heterogeneous strains, resistance to inactivation, and spread by cellular transport mechanisms. These features define the broad limits of prion pathobiology within the context of the core definition – ‘proteins that acquire alternative conformations that become self-propagating’5 – and as we and others have found, many of the ancillary qualities associated with prions also are not unique to the prion protein. Here we consider, point by point, how key attributes of Aβ seeds compare to those of PrP-prions.

**Aβ seeds and PrP-prions are rich in β-sheet and prone to forming amyloid**

PrPSc has an enhanced tendency to form amyloid,6,14 a general state in which a β-sheet-rich misfolded protein polymerizes into fibrils that yield a characteristic X-ray diffraction pattern, and that further coalesce into masses with
distinctive histologic staining patterns.\textsuperscript{14,15} Although the misfolded state imparts important functional capacities to PrP-prions, the formation of amyloid is not mandatory for the induction of disease.\textsuperscript{16-18} Indeed, PrP-prions are heterogeneous entities; PrP can assume alternative conformations with varying properties (‘strains’; see below), and PrP\textsuperscript{Sc} assembles into a spectrum of bioactive multimers that range from small oligomers to large amyloid fibrils.\textsuperscript{19}

Using the dye Congo red, Divry first reported the amyloid nature of senile plaques in AD nearly a century ago.\textsuperscript{20} In the 1980s, the amyloidogenic protein in Alzheimer plaques and cerebral amyloid angiopathy (CAA) was identified as what is now known as A\textsubscript{\beta},\textsuperscript{21,22} and around the same time the amyloid deposits that are present to varying degrees in prion diseases were found to consist of PrP.\textsuperscript{23} In addition to Congo red, newer amyloid-specific dyes such as the luminescent conjugated oligothiophenes (LCOs) have been used to characterize deposits of A\textsubscript{\beta} and PrP in tissue sections.\textsuperscript{24-26} These dyes derive their selectivity for amyloid from their interaction with the \(\beta\)-sheet-rich regions of misfolded protein complexes, and as such they have been helpful in defining polymorphic amyloid strains.\textsuperscript{26,27} Although misfolded A\textsubscript{\beta} frequently forms amyloid in AD, as in prion disease, amyloid \textit{per se} is not obligatory for the manifestation of Alzheimer’s disease (more on this below).

\textbf{A\textsubscript{\beta} seeds and PrP-prions are resistant to inactivation}

Owing to the stability conferred by the amyloid state, PrP-prions can be remarkably resistant to physicochemical degradation, a quality that contributes to their persistence and infectivity, and therefore has important public health implications.\textsuperscript{28} Both PrP-prions and A\textsubscript{\beta} seeds are resistant to inactivation by heat and formaldehyde.\textsuperscript{28-31} Furthermore, both agents are extraordinarily long-lasting in the living brain; when A\textsubscript{\beta} seeds were infused into the brains of APP-knockout mice (which are incapable of replicating the seeds), some seeding-competent A\textsubscript{\beta} remained even after 6 months in the recipients.\textsuperscript{32} Similarly, PrP-prions have been reported to retain their infectivity after nearly 20 months in the brains of hosts incapable of replicating prions.\textsuperscript{33} Additionally, aggregated A\textsubscript{\beta} is resistant to degradation by proteases,\textsuperscript{34} similar to PrP-prions (for which this property is exploited in the diagnostic detection of disease).\textsuperscript{35} However, analysis of the A\textsubscript{\beta}-inducing species revealed that small, soluble seeds harbor considerable amyloid-inducing activity, and that these small seeds are readily inactivated by proteinase-K,\textsuperscript{34,36} comparable to the high specific activity,\textsuperscript{19} and proteinase K-sensitivity of oligomeric forms of PrP.\textsuperscript{37}

\textbf{A\textsubscript{\beta} Seeds and PrP-prions Propagate by Molecular Templating}

Earlier \textit{in vitro} studies demonstrated that preformed A\textsubscript{\beta} seeds are able to convert monomeric A\textsubscript{\beta} into extended fibrils by molecular conformational templating (i.e., seeding).\textsuperscript{38} A series of experiments in transgenic mouse models expressing human-sequence APP showed that infusion of small amounts of brain extracts containing aggregated A\textsubscript{\beta} can induce the formation of plaques and CAA \textit{in vivo}, and that aggregated A\textsubscript{\beta} is essential for the seeding effect (see ref.39 for review). Similar to PrP-prion seeding, the A\textsubscript{\beta}-seeding effect can be achieved \textit{de novo} in rodent models in which such pathology is not normally seen within the average lifespans of the animals.\textsuperscript{40,41}

\textbf{Misfolded A\textsubscript{\beta} and PrP Aggregate into Variant, Inducible Strains}

The identification of structurally and functionally distinct prion strains has helped to explain how the pathobiology of these molecules is influenced by their architecture, beyond the linear amino acid sequence. PrP-prions can misfold and assemble into seeds with varying structural and functional features that can be passed on to subsequent generations of prions.\textsuperscript{42} Different prion strains also spur specific spatiotemporal patterns of PrP-deposition, while at the same time producing distinct
neurodegenerative phenotypes that are encoded by their biochemical fingerprint.43

Analogously, Aβ can misfold and assemble into strain-like structural variants both in vitro and in vivo.44-52 To determine whether the structural properties of Aβ can be seeded in new hosts, cross-seeding experiments were undertaken in two transgenic mouse lines that develop phenotypically dissimilar patterns of Aβ distribution and plaque size as they age.29 Intracerebral inoculation of brain extract from one mouse line into the other engendered seeded plaques that were morphological hybrids of the predominant plaques generated by the donor and the host.29 Subsequent experiments using conformation-sensitive LCOs showed that the fluorescence spectra emitted by cross-seeded plaques differed from the spectra emitted by endogenous, unseeded plaques in the same transgenic mouse lines.51

These findings were confirmed and extended in an ex vivo hippocampal slice culture model in which the morphology and LCO-spectral signatures of seeded plaques were influenced by the mouse line that furnished the initial seed as well as the isotype of Aβ added to the medium.53 The strain-like differences in seeded plaques on the hippocampal slices were associated with different ratios of the two commonly generated Aβ isoforms of 40 and 42 amino acids (Aβ40 and Aβ42), as had been seen in the in vivo cross-seeding experiments.51 Other studies have found that Aβ40 and Aβ42 differentially influence the strain type, and that distinct strain-like features of synthetic Aβ seeds created in vitro are retained after in vivo passage.48

Aβ deposits in humans with AD can differ in terms of morphology,54 ligand binding,55 solid-state nuclear magnetic resonance signature,56 and biophysical attributes such as conformational stability.52 In an initial study, brain samples from two AD patients with dissimilar clinical histories were used to seed the aggregation of synthetic Aβ40 in vitro, and the resulting Aβ fibrils showed distinct nuclear magnetic resonance and electron-microscopic characteristics.50 The authors proposed that a single, dominant Aβ structure is propagated by seeded nucleation in each brain, and that this molecular structure influences clinical progression. In a larger cohort of patients, these findings were extended to show different molecular configurations of Aβ assemblies in rapidly progressing AD cases compared to normally progressing cases.56 Similarly, different rates of cognitive decline have been correlated with distinct conformations of Aβ42.57 These experiments suggest that rapidly progressing AD may be associated with a particularly virulent strain of misfolded Aβ.

An alternative Aβ strain also has been implicated in a hereditary type of AD linked to a mutation within the Aβ sequence (E22G; the “arctic” mutation). These patients harbor Aβ plaques with a core largely devoid of amyloid; when brain extracts from arctic AD patients were injected into APP23 transgenic mice (which express the non-mutant sequence of human Aβ), cerebral blood vessels were surrounded by unusual fuzzy Aβ deposits, unlike the CAA in mice seeded with extracts from non-arctic AD cases.49,58 In addition to reinforcing the Aβ-strain hypothesis, studies of arctic-mutant Aβ underscore the important (and often unrecognized) point that, while Aβ aggregation is central to AD, classical amyloid deposits are not obligatory for the clinical expression of the disease. Collectively, these experiments show that, like PrP-prions, particular strains of aggregated Aβ can be propagated in vitro and in vivo by molecular templating. While the existing evidence strongly indicates that Aβ structure is associated with disease phenotype, the critical link between the pathophysiological traits and molecular architecture of Aβ have not yet been fully defined.

Aβ Seeds and PrP-prions Translocate within and to the Brain

Intraocular injection of PrP-prions has shown that the agent can be conveyed from one part of the nervous system to another by neural transport mechanisms.59-62 Similarly, Aβ seeds introduced focally into the brain induce Aβ aggregation that propagates systematically to interconnected regions.63,64 In vitro studies indicate that the trafficking of Aβ seeds is
mediated by neuronal uptake, transport and release mechanisms.\textsuperscript{65,66} Within cells, soluble Aβ is concentrated in the acidic environment of endosomes/lysosomes, where it assembles into higher molecular weight seeds.\textsuperscript{67} There is also evidence that membrane-associated, non-fibrillar Aβ in mitochondria has robust seeding capacity.\textsuperscript{68} Notably, placement of Aβ seeds into the peritoneal cavity is capable of inducing Aβ deposition in the brain,\textsuperscript{69,70} though the mechanisms involved in the translocation of the seeds from periphery to brain are uncertain. These findings demonstrate the extensive mobility of Aβ within and outside of the CNS, with implications for the iatrogenic induction of Aβ aggregation in humans (below).

\textbf{Aβ Seeds can Induce Aβ Deposition in Humans}

Despite longstanding experimental evidence for the prion-like seeding of Aβ \textit{in vitro} and \textit{in vivo}, the relevance of the seeding paradigm to humans has been uncertain. Recent studies aimed at bridging this gap have involved the opportunistic evaluation of Aβ pathology in tissues from patients who had been treated with human cadaver-derived growth hormone or dura mater implants.\textsuperscript{71-75}

In the first such investigations, the patients who were analyzed had died of iatrogenic Creutzfeldt-Jakob disease (iCJD) years after having received cadaveric growth hormone or dura mater; hypothesizing that the treatment materials were also likely to have harbored Aβ seeds from donors who had died with AD (or incipient AD), the researchers demonstrated that recipients who contracted iCJD also had significantly greater cerebral Aβ deposition than did control patients.\textsuperscript{71-74} The link between cadaveric growth hormone treatment and Aβ deposition was subsequently confirmed in a larger cohort of iCJD patients; significantly, increased Aβ deposition also occurred in hormone recipients who died of causes other than CJD, indicating that the Aβ deposition is not caused by the prionopathy.\textsuperscript{75}

A noteworthy caveat in these analyses is that the patients with Aβ pathology did not have AD-like tauopathy at the time of death, and thus they did not fulfill the pathologic criteria for fully developed AD. This is surprising for two reasons; first, experimental work has demonstrated that aggregated Aβ is capable of inciting tauopathy in experimental animals,\textsuperscript{76} and that Aβ can cross-seed tau assembly to produce potent, \textit{in vivo}-active tau seeds.\textsuperscript{77} Second, pituitaries that contained Aβ seeds are likely to have contained tau seeds as well,\textsuperscript{78} and tau itself can be induced to misfold and polymerize in a prion-like fashion;\textsuperscript{79} hence, if tau seeds survived the purification process and entered the brain (neither of which is known), a direct tau seeding effect would have been expected. Further scrutiny of the cadaveric growth hormone and dura mater recipients will be needed to determine whether tauopathy might also be inducible in humans.

The implications of these findings for the risk of AD in surviving recipients of human-derived growth hormone and dura mater transplants are ambiguous. A study of growth hormone recipients in the US found no evidence of an increased incidence of AD as of 2008,\textsuperscript{78} but the growth hormone preparations in the US included a stringent purification step after 1977 that likely eliminated most PrP-prions.\textsuperscript{80} Since no cases of iCJD have occurred in US patients treated after 1977, it is possible that these recipients also would be less likely to have been exposed to Aβ (or tau) seeds. In addition, because the analyzed recipients of tainted biologics had died of CJD or other causes at relatively young ages,\textsuperscript{71-75} it is not possible to know whether they would have developed AD after a longer incubation period, especially given that Aβ deposition begins in the AD brain decades before the emergence of cognitive decline.\textsuperscript{81} It is worth noting that the kinetics of protein misfolding and aggregation are likely to be important for the effective transmission of proteopathies, and differences in kinetics could explain the potency of exogenous PrP-prions at eliciting disease compared to Aβ in similar exposure scenarios.

Improvements in the production and preparation of biologic agents have essentially eliminated the risk of iatrogenic CJD.\textsuperscript{80} However, longer-term follow-up of patients who received
cadaveric growth hormone and dura mater transplants during this problematic period is needed to establish the risk of AD with certainty. In light of evidence for the seeded induction of Aβ deposition and the cerebral invasion of peripheral Aβ seeds in animal models,69,70 there is also a need for more extensive surveillance of Aβ pathology that might be linked to other sources such as blood and blood products.

The Most Effective Aβ Seeds and PrP-prions are Generated in Vivo

Finally, it is worth highlighting the puzzling observation that both Aβ seeds and PrP-prions are most potent when generated in living tissues. Initial investigations of Aβ seeding in mouse models demonstrated that brain extracts containing aggregated Aβ strongly induce Aβ deposition, whereas synthetic Aβ that was pre-aggregated in vitro was ineffective within the same incubation timeframe.29 Subsequent studies employing a longer incubation period showed that synthetic Aβ seeds can induce deposition in APP-transgenic mice, albeit with low potency relative to brain-derived seeds.82 Generating efficacious PrP seeds in vitro also has been a persistent challenge, but aggregation of recombinant PrP in the presence of specific co-factors can markedly increase their infectivity.83 Likewise, when synthetic Aβ is aggregated on living tissue slices in culture, the resulting Aβ seeds induce robust Aβ deposition in vivo.53 Determining why proteinaceous seeds that develop in living tissues are more potent than seeds aggregated in vitro is an important objective for future research.

CONCLUSIONS AND OPEN QUESTIONS

The original definition of prions as proteinaceous infectious particles84 has hindered the expansion of the prion concept to other proteopathies, in part because of concern that these diseases might be perceived as contagious under everyday circumstances.3 For this reason, and because prion-like mechanisms are increasingly recognized in many realms of biology,11-13,85-89 we have argued that ‘proteinaceous nucleating particles’ would serve as a more inclusive (and less alarming) definition of prions.3 Aβ seeds undoubtedly meet the key criteria to qualify as prions, and evidence is growing that the prion paradigm includes several other proteopathies as well.3,5,6,79 However, many issues require resolution; among these: What is the connection between seeding capacity and toxicity? How do the conformation and size of aggregating proteins influence their pathobiology? How is Aβ linked to tauopathy in the AD cascade? Do different Aβ strains explain the resistance of non-human species (and perhaps some humans) to AD?90 What factors influence the conversion of pathogenic proteins to a prion-like state? How are the proteins processed and transferred by cells? And given growing evidence for prion-like processes in a wide spectrum of diseases, how can the expanded prion principle help to unify the search for new therapeutic objectives?

ABBREVIATIONS

| Term          | Abbreviation |
|---------------|--------------|
| Aβ            | amyloid-β    |
| AD            | Alzheimer’s disease |
| APP           | Aβ-precursor protein |
| CAA           | cerebral amyloid angiopathy |
| CJD           | Creutzfeldt-Jakob disease |
| iCJD          | Iatrogenic Creutzfeldt-Jakob disease |
| LCO           | luminescent conjugated oligothiophene |
| PrP           | prion protein |
| PrPSc         | prion protein scrapie, PrP in a pathogenic conformation |

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

There are no conflicts of interest to declare.

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