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Prion-like Mechanisms in Neurodegenerative diseases: I. Alzheimer's disease

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Abstract

The two principal histopathologic hallmarks of Alzheimer's disease (AD), senile plaques and neurofibrillary tangles, are structurally abnormal variants of normally generated Aβ and tau proteins. Both proteins share five key properties with classic prions, i.e., auto-propagation, self-assembly of like proteins, manifestation as polymorphic and polyfunctional strains, resistance to chemical and enzymatic destruction, and spreading ability within the brain and from the periphery to the brain. For this reason, AD was dubbed a double-prion disease although this is not universally accepted – other researchers rather refer to it as a double-prion-like disease. In AD, the pathogenic cascade follows the sequential corruption of Aβ and then tau. In this article, after a brief review of AD, the prion paradigm amyloid and AD neuropathology will be set forth, and the prion-like properties of the AD proteins will be discussed. The therapeutic implications of the prion paradigm will lastly be addressed, including the three options of reducing the production of the proteins, uncoupling the Aβ-tauopathy connection, or promoting the inactivation or removal of anomalous assemblies from the brain. However, while the double-prion hypothesis is significant, especially as it offers new approaches to treatment, it does not reach to the cause of AD and may not result in a cure.

Abbreviations

Aβ: Amyloid beta; AD: Alzheimer's disease; ApoE: Apolipoprotein E; APP: Aβ-precursor protein; CAA: Cerebral amyloid angiopathy; c-hGH: cadaver-derived human growth hormone; CJD: Creutzfeldt-Jakob disease; CSF: Cerebrospinal fluid; DSM: Diagnostic and Statistical Manual of Mental Disorders; MCD: Mad cow disease; SBE: Spongiform bovine encephalopathy; NDD: Neurodegenerative diseases; NIH: (U.S.) National Institutes of Health; PrP: Prion protein; UCSF: University of California, San Francisco

Keywords

Alzheimer's disease; Amyloid beta protein; Creutzfeldt-Jakob disease; Double prion hypothesis; Prions; Prion disorders; Prion protein; Tau protein.

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One of the most feared hazards of growing old is the profound deterioration of mental faculties known as dementia. Dementia can be defined as "a decline from a person's previously established level of intellectual function that is sufficient to interfere with the everyday performance of that individual". Based on the criteria set forth in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), dementia due to AD is defined as "the insidious onset and gradual progression of substantial impairment in learning and memory and at least one other cognitive domain (complex attention, executive function, language, perceptual-motor, or social cognition) that interferes with independence in everyday activities". An important feature of these definitions is that the impairments are substantial and, thus, become incapacitating even under ordinary circumstances.

On Alzheimer's disease

Alzheimer's disease (AD) is currently defined based on the presence of toxic protein aggregations in the brain known as 'amyloid plaques' and 'tau tangles', accompanied by cognitive decline and dementia. But attempts to treat the disease by clearing out these inert proteins have been unsuccessful. New evidence that active Aß and tau prions could be driving the disease could lead researchers to explore new therapies that focus on prions directly. However, despite its potential for new therapies, it is important to note that this prion paradigm is not the root cause of the disease although it provides its driving forces and mechanisms. As of this writing, that root cause remains the explanation provided by this author, namely that AD (and other neurodegenerative diseases) is (are) but a rogue autoimmune disease (s).

More than 50 different conditions are associated with dementia, but of these, AD is the most common, accounting for nearly 60-70% of the total of cases. In 2021, globally, 57 million live with dementia, a number projected to reach 78 million by 2030 and 153 million by 2050 with a new case diagnosed every 3 seconds. About 10 million new cases of dementia are diagnosed each year globally. In 2022, a (U.S.) National Institutes of Health (NIH) study estimated that 32 million people worldwide have AD dementia, with an additional 69 million in the prodromal stage and 315 million in the preclinical stage, totaling 416 million people across the continuum.

Around 60% of people with dementia currently live in low and middle-income countries, a figure expected to rise to 71% by 2050. The prevalence of dementia increases significantly with age. In some developed nations, about 1 in 10 people aged 65 or older are affected, while more than one-third of those 85 or older may have symptoms. AD and other dementias are more prevalent in women than men, especially in those aged 65 and over. Up to three-quarters of individuals with dementia worldwide have not received a diagnosis. The social and economic costs of the disease will rise accordingly, with an ever-greater burden of caring for afflicted persons falling on younger generations. Disease-modifying treatments are urgently needed, but these can only emerge from a deep understanding of AD itself.

As the average life expectancy of populations grows in many parts of the world, and in the absence of an effective prevention or treatment, as many as 115 million people are expected to have AD in the year 2050. The incidence and prevalence of AD double every 5 years between the ages of 65 and 95. While the exact number with only AD is hard to pinpoint, it is the most

common form of dementia and accounts for a significant majority of cases.

Signs, symptoms, and risk factors

AD typically begins with the gradual onset of mild cognitive impairment (MCI), progressing inexorably to dementia with an average clinical duration of 7–10 years (although the time course is variable). The signs and symptoms shown by individual patients also can vary substantially, but the diagnosis of AD is established by the universal presence of core attributes, specifically progressive dementia in the context of characteristic lesions in the brain: senile (Aβ) plaques and neurofibrillary (tau) tangles, two of the main hallmarks of the disease. A defining pathologic feature of AD is the abnormal accumulation in the brain of these two proteins. As elaborated below, recent evidence shows that this process is initiated and sustained by a prion-like mechanism of seeded protein aggregation.

The probability of developing AD is influenced by several factors:

• **Genetic risk factors:** They include rare causative, autosomal dominant mutations with essentially complete penetrance, as well as diverse genetic polymorphisms that modulate risk to varying degrees. Autosomal dominant mutations associated with AD all occur in the genes that code for the Aβ-precursor protein (APP) or for presenilin-1 or presenilin-2 (the presenilins being key components of intramembranous protease complexes that liberate Aβ from APP). The gene encoding APP is on chromosome 21, and the genes encoding presenilin-1 and presenilin-2 are on chromosomes 14 and 1, respectively. Dominant and recessive genetic causes account for less than 1% of all AD cases. An exception is the gene that encodes apolipoprotein E (ApoE), a protein that mediates lipid transport throughout the body and is the major apolipoprotein in the brain. The three major protein isoforms of ApoE in human populations are ApoE2, ApoE3 and ApoE4. The most frequent isoform is ApoE3 (~78%), followed by ApoE4 (~14%) and ApoE2 (~8%). Bearers of the ApoE4 allele have an allele-dose-dependent increase in the risk of AD. The mechanism by which ApoE4 predisposes carriers to AD is probably multifaceted, but it is known that bearers of ApoE4 begin to accumulate Aβ in the brain at least a decade earlier in life than do non-bearers. Thus, ApoE4, like the known dominant and recessive genetic risk factors, appears to augment the probability of developing AD by advancing the onset of the Aβ cascade. Indeed, all known AD-linked mutations affect the production, removal, trafficking, or aggregating tendency of Aβ.

• **Other risk factors:** In addition to the genetic risk factors for AD, numerous environmental and endogenous risk factors have been identified. These include advancing age, traumatic brain injury, diabetes and metabolic disorders, inflammation, vascular disorders, gender, and lifestyle. In some instances, these should be considered as risk factors for dementia, broadly defined, rather than for AD per se. For example, multiple small infarcts might raise the likelihood of dementia independently of AD, or they may advance the onset of dementia in people who also are incubating AD pathology in the brain.

Differential diagnosis and biomarkers

Until recently, senile plaques and neurofibrillary tangles could only be identified by microscopic analysis of brain samples, but increasingly sensitive and specific diagnostic tests are emerging that enable the detection of proteopathic abnormalities in living subjects. These include radiolabeled imaging agents for Aβ and tau in the brain, and assays for quantitation of the proteins in the cerebrospinal fluid (CSF), and new blood tests. Investigations of these biomarkers indicate that the disease process begins two decades or more before the onset of demonstrable cognitive impairment. In addition, the presence of genetic risk factors such as the ε4 allele of apolipoprotein E (ApoEε4) can reinforce the

in-life diagnosis of AD.

It is important to place AD in the context of other brain changes that impair intellectual capacities in the elderly. In younger patients with autosomal dominant causes of AD, the disease is relatively unambiguous histopathologically, i.e., lesions other than plaques and tangles are rare. With advancing age, additional disorders are increasingly likely to contribute to dementia, including cerebrovascular disease, hippocampal sclerosis, and such cerebral proteopathies as α-synucleinopathy, TDP-43 proteopathy, and others. These maladies can cause dementia on their own, but they also sometimes co-exist with AD, complicating diagnosis, exacerbating the clinical course, and likely diminishing the effectiveness of treatments directed at only one of the conditions. In addition, potentially reversible causes of a dementia-like state must be ruled out, such as depression, infections, drugs and drug interactions, thyroid dysfunction, tumors, and vitamin B12 deficiency, as intervention in these instances might at least partially restore cognitive function.

Why is Alzheimer's called a double-prion disease?

AD is considered a "double-prion" disorder because it involves the self-propagating, misfolding nature of both amyloid-beta (Aβ) and tau proteins. However, unlike traditional prion diseases, Alzheimer's is not considered contagious through normal interpersonal contact. The concept of a double-prion disorder hinges on the behavior of two key proteins already indicated earlier:

- Amyloid-beta (Aβ) prions: These are misfolded Aβ peptides that can induce normal Aβ proteins to also misfold. This triggers a cascade of aggregation that leads to the formation of amyloid plaques in the brain.
- Tau prions: Pathological tau proteins can seed the misfolding of normal tau proteins, leading to their accumulation in neurofibrillary tangles. The spread of tau pathology through the brain is believed to follow anatomically connected regions.

In AD, both "prion-like" activities occur, destroying neurons together.

Distinctions from classic prion diseases

The “double-prion” model is a debated concept because AD lacks certain characteristics of classic prion diseases like Creutzfeldt-Jakob disease (CJD), specifically:

- **Transmission:** Classic prion diseases are infectious and can be transmitted through exposure to contaminated tissue. While studies have shown that Aβ and tau aggregates can be experimentally transmitted in animals and, in rare historical cases, between humans via contaminated growth hormone or surgical instruments, AD is not considered contagious.

- **Speed of progression:** Prion diseases typically progress very quickly and are rapidly fatal. The spread of Aβ and tau in Alzheimer's is considerably slower.

The prion paradigm amyloid and AD neuropathology

AD is best understood as a dual-protein, prion-like disorder because two different proteins—β-amyloid (Aβ) and tau—misfold, self-propagate, spread through the brain in a prion-like manner, and interact and drive neurodegeneration. This “double prion” view explains why AD is progressive, network-specific, and difficult to halt once established while remaining non-contagious under ordinary conditions. However, unlike classical prion diseases (e.g., Creutzfeldt–Jakob disease), AD is not contagious in everyday life, but the underlying mechanism of pathology progression shows striking parallels.

As in the case of most proteopathies, the proteins

implicated in the development of AD are structurally abnormal manifestations of proteins that are normally generated by cells. The abnormalities often involve an altered 3-dimensional architecture (misfolding), which can be promoted by amino acid substitutions, post-translational modifications, sequence expansions or truncations, and such characteristics of the local milieu as temperature and pH. In addition, factors that increase the concentration of certain proteins (e.g., by raising their production or impairing their removal/degradation) can elevate the risk of disease. A frequent indication that a protein is structurally corrupted at the molecular level is its enhanced tendency to form amyloid. In general, amyloid is a state in which a protein accumulates in tissues as masses of ~10nm-diameter fibrils. Within the brain, it is not uncommon to find some degree of Aβ-amyloidosis and tauopathy in the elderly; in those with dementia, abundant Aβ plaques and tau tangles are the two types of amyloid that are pathognomonic for AD.

Figure 1 illustrates the neuropathologic features of AD, which include senile (Aβ) plaques (reddish brown) and neurofibrillary (tau) tangles (black). The formation of amyloid by Aβ and tau is an obvious sign of a proteopathic process, but small oligomeric assemblies may be the more toxic form of the proteins. Aβ in the amyloid state is virtually always present in AD, but an instructive exception is a rare hereditary type of AD caused by a mutation that changes glutamate to glycine at position 22 of Aβ (E22G; the 'arctic' mutation). This mutation results in early-onset AD in which Aβ plaques lack the prototypical amyloid cores, indicating that 'amyloid' in the strict sense is not required to drive the Aβ-cascade.

There can be little doubt that Aβ is a driving force in the genesis of AD, or that β-amyloid accumulation per se is detrimental to cognition, particularly when embodied as neuritic plaques. However, tauopathy is an essential downstream consequence that correlates more strongly with the degree of dementia than does the number of Aβ plaques. In AD and other tauopathies, tau misfolds and becomes hyperphosphorylated; like Aβ, the altered tau molecules aggregate to form soluble oligomers and long β-sheet-rich polymers that have the characteristics that define amyloids. The tau fibrils bundle together as neurofibrillary tangles in neurons, although tauopathy also can afflict glial cells. Tauopathy occurs in association with many brain disorders besides AD. The primary tauopathies are disorders in which tau aggregation is the major abnormality.

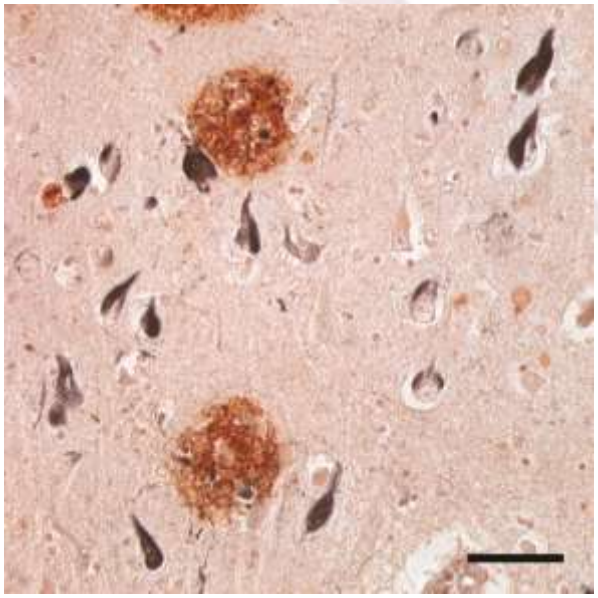

Figure 1: The two types of amyloids in AD

Evidence for the "double prion" concept

Five pieces of evidence mitigate for the double prion concept:

1. Misfolding and seeding:
• Aβ and tau both misfold into abnormal conformations.
• Misfolded proteins seed normal molecules to adopt the same structure.
• In animal and cell models, introducing misfolded Aβ or tau accelerates pathology.
2. Human tissue seeding activity:
• Biosensor cell assays detect tau and Aβ seeding activity in brain samples from AD patients.
• Even low-level seeding is measurable, confirming prion-like behavior.
3. Network spread:
• Pathology follows functional brain networks, not just local spread.
• This matches Braak staging wherein tau pathology advances through synaptically connected regions.
4. Quantification of Aβ and tau prions:
• Studies at the University of California at San Francisco (UCSF) and elsewhere have directly measured self-propagating Aβ and tau assemblies in Alzheimer diseased brain tissue.
• These findings frame AD as a "double prion" disorder.
5. Rare transmission events:
• Historic cases (recipients of cadaver-derived growth hormone) developed Aβ deposits and AD-like symptoms decades later.

• Seeds can transmit under unusual medical

circumstances → extracellular plaques → spreads via interstitial pathways.

• Tau → intracellular tangles → spreads via synaptic

connectivity.

• The combined effect of Aβ and tau → progressive

network failure → cognitive decline.
• Historic cases (recipients of cadaver-derived growth hormone) developed Aβ deposits and AD-like symptoms decades later.

• Seeds can transmit under unusual medical

circumstances → extracellular plaques → spreads via interstitial pathways.

• Tau → intracellular tangles → spreads via synaptic

connectivity.

• The combined effect of Aβ and tau → progressive

network failure → cognitive decline.
• **Importantly:** No evidence of person-to-person contagiousness in daily life.
As a result, the experts' consensus is:
• AD progression involves prion-like seeding and spread of two distinct proteins.
• The term "double-prion-like disorder" emphasizes this dual mechanism.
• However, AD remains biologically distinct from classical infectious prion diseases.

Extended neuropathology of AD

In addition to the Aβ plaques and tau tangles in AD, other changes are present in the brain that complicate the disease phenotype. One is the accumulation of Aβ in and around the walls of cerebral blood vessels, a condition known as Aβ-type cerebral amyloid angiopathy (Aβ-CAA). Aβ-CAA weakens the vascular wall and elevates the risk of intracranial hemorrhage. Like Aβ plaques and tauopathy, Aβ-CAA is not specific to AD, and its prevalence increases with advancing age. However, some degree of Aβ-CAA is almost always present in AD, being severe in around 25% of cases. It must be noted that the factors that drive the inconsistent occurrence of Aβ-CAA in different people remain uncertain.

Other neurodegenerative conditions might be present in the brain along with the lesions of AD, particularly in older patients. They are found to variable extents among

end-stage AD cases, and most of these anomalies lack diagnostic specificity for the disease. Macroscopically, loss of brain tissue and concomitant expansion of the association with Aβ plaques, as well as increased inflammatory mediators such as cytokines. Granulovacuolar degeneration, perisomatic granules and Hirano bodies may be present, but their significance for AD per se is uncertain. Many different neuronal systems are compromised in AD, some more markedly than others, and synapses are regionally depleted. In some cases of AD, spongiform change is evident that, though generally less severe, can resemble that seen in Creutzfeldt-Jakob disease (CJD). Figure 2 contrasts the spongiform change (vacuoles, seen in these micrographs as white holes) in the neocortex of an AD patient (A) and in a patient with CJD (B). Spongiform change is not unique to prion diseases, but it is less common in AD, and when it occurs it is generally mild.

ventricles are common, but this varies among regions and among patients. Evidence of inflammation includes reactive microglia and astrocytes, especially in

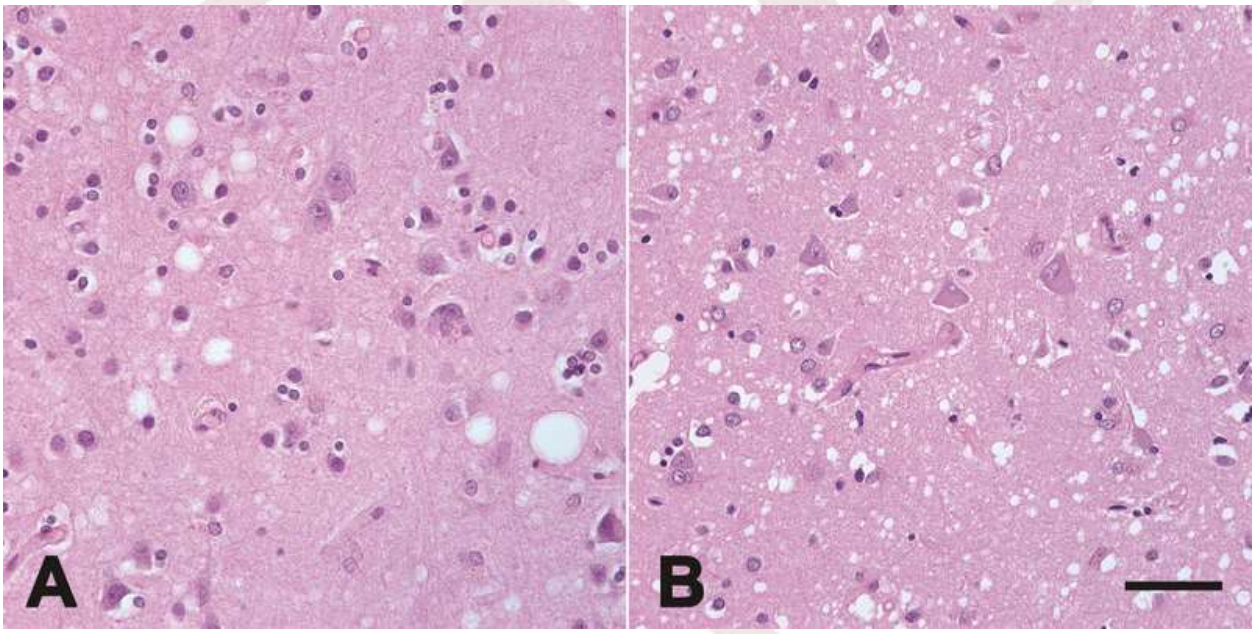

Figure 2: Contrasting the spongiform change in the neocortex of an AD patient with a CJD patient

Regardless of the complexity of damage to the brain, the essential and unifying feature of AD is the obligatory presence of aggregated Aβ and tau proteins. For this reason, extensive research has been directed toward determining how the proteins misfold, self-assemble, and propagate their pathogenic features, a process that shares important commonalities with the molecular pathogenesis of prions.

Prion-like properties of AD proteins

What are prions?

Prions are misfolded versions of a protein that can spread like an infection by forcing normal copies of that protein into the same self-propagating, misfolded shape. The original prion protein, PrP, was identified by Prusiner in the 1980s as the cause of Creutzfeldt Jakob Disease (CJD) and spongiform bovine encephalopathy (SBE), also known as mad cow disease (MCD), which spread through consumption of meat and bone meal

tainted with PrP prions. This was the first time a disease had been shown to infect people not by an infestation of an organism such as a bacterium or a virus, but through an infectious protein. Prusiner received a Nobel Prize for that discovery in 1997.

Prusiner and colleagues have long suspected that PrP was not the only protein capable of acting as a self-propagating prion, and that distinct types of prions could be responsible for other neurodegenerative diseases (NDDs) caused by the progressive toxic buildup of misfolded proteins. Indeed, for example, laboratory studies at the UCSF and elsewhere have shown that the Aß amyloid plaques and the tau tangles from diseased brains (the hallmarks of AD) can infect healthy brain tissue much like PrP, but considerably more slowly.

Many scientists have been reluctant to accept that Aß and tau are self-propagating prions — instead referring to their spread as "prion-like" — because unlike PrP prions, they were not thought to be infectious except in highly controlled laboratory studies. However, recent reports have documented rare cases of patients treated with growth hormone derived from human brain tissue, or given transplants of the brain's protective dura mater, who went on to develop Aß plaques in middle age, long before they should be seen in anyone without a genetic disorder. Prusiner contends that these findings argue that both Aß and tau are prions even though they propagate more slowly than highly aggressive PrP prions.

Previously, Alzheimer's research has been stuck looking at collateral damage in the form of misfolded, dead proteins that form plaques and tangles. Now, it turns out that it is prion activity that correlates with disease, rather than the number of plaques and tangles at the time of autopsy. So, to succeed in developing effective therapies and diagnostics for AD, we need to target the active prion forms rather than the large amount of protein in plaques and tangles.

Prion-like properties of aggregated Aβ

The idea that AD might arise by a pathogenic mechanism similar to that of prion diseases has a fairly long history, dating back to the early 1980s. Based on their success in transmitting kuru and CJD to nonhuman primates, and on the hypothesis that a 'slow virus' might be involved in other neurodegenerative disorders, researchers were able to experimentally transmit AD to several species of nonhuman primates. Experiments were also initiated to explicitly test the hypothesis that Aβ can be induced to aggregate in the living brain by a prion-like mechanism. These studies showed that Aβ plaques and CAA are seedable by brain extracts from AD patients, but not by extracts derived from control brains that were devoid of aggregated Aβ.

Subsequent experiments showed unequivocally that the active agent is aggregated Aβ, and that the ability of Aβ to seed as well as the characteristics of the resulting deposits are governed by both the agent and the host. These findings have been confirmed and extended by other laboratories and the collective experiments have established that the molecular features of Aβ seeds are essentially the same as those that define the pathogenicity of prions. Key commonalities between Aβ seeds and PrP-prions are summarized as follows:

1. The active seeding agent is a form of the protein itself. The degree of Aβ-seeding is directly related to the concentration of Aβ in the brain and even extremely small amounts of Aβ seeds can stimulate aggregation in the brain. Synthetic, pre-aggregated Aβ can seed deposition, albeit relatively weakly.

2. Aβ seeds are rich in β-sheet secondary structure. Amyloid fibrils of all types, including Aβ-amyloid and PrP-amyloid, are rich in β-sheets in which the individual β-strands run approximately perpendicular to the

long axis of the fibrils.

3. Misfolded Aβ can manifest as structurally and functionally variant strains. As in the case of PrP-prions, Aβ can fold into strain-like variants both in vitro and in vivo. Cerebral Aβ assemblies in humans with AD vary in terms of plaque morphology, ligand binding characteristics, solid-state nuclear magnetic resonance features as well as conformational stability and other biophysical characteristics.

4. Seeds vary in size and sensitivity to proteinase K. Infectious PrP-prions exist in a wide range of sizes, the most potent of which are small and soluble. Similarly, Aβ seeds can range from large fibrils to small, oligomeric seeds with high biologic potency.

5. Some Aβ seeds are durable. Like PrP-prions, Aβ seeds retain their potency in donor brain tissue that has been in formaldehyde for years. Aβ seeds also are durable within the living brain; they retain some bioactivity (albeit with progressively diminishing potency) for at least 6-months after infusion into the brains.

6. Aβ seeds spread systematically within the brain. As with PrP-prions and other proteopathic seeds, Aβ seeds introduced into one part of the brain induce protein aggregation that spreads systematically to interconnected regions. In cell culture experiments, Aβ seeds were demonstrated to spread by transfer from neuron to neuron, and neuroanatomical patterns of deposition are consistent with spread along neuronal pathways.

7. Aβ aggregation can be instigated de novo. Animal studies indicate that Aβ deposition is inducible de novo, and in this paradigm is not simply an acceleration of an ongoing process.

8. Aβ proteopathy is serially transmissible. Like PrP-prions, different strains of Aβ seeds can be successively transmitted from the initially seeded mice to subsequent hosts.

Notwithstanding the above long list of key commonalities between Aβ seeds and PrP-prions, open questions remain regarding the prion-like properties of Aβ:

1. The conditions that influence protein aggregation, seeding, and toxicity in living systems need to be clarified. Such clarification could disclose new therapeutic objectives for multiple proteopathies.

2. The reasons for the poor seeding efficiency of CSF Aβ are unknown and need to be elucidated. The Aβ assemblies in CSF are smaller and mostly devoid of N-terminally truncated variants compared to brain-derived Aβ. Other substances in the CSF, such as cystatin C, might interfere with the seeding capacity of multimeric Aβ.

3. The implications of the Aβ-PrP interaction for AD appear to be complex. Its impact on Aβ toxicity or aggregation may be either deleterious or beneficial.

Prion-like properties of aggregated tau

At the ultrastructural level, neurofibrillary tangles in AD consist predominantly of characteristic paired helical filaments that result from the ectopic polymerization of hyperphosphorylated tau protein. Tau-hyperphosphorylation is thought to be an early stage in the formation of tangles. Like Aβ-proteopathy and prion disease, tauopathy can be induced in the brain by tau seeds that have been infused into the peritoneal cavity, and bioactive tau seeds exist in a range of sizes. Brain extracts from donors with clinicopathologically distinct human tauopathies induce tau lesions in host mice that resemble the lesions in the corresponding human disorders, indicating that tau, like Aβ and PrP, can misfold into replicable proteopathic strains. Tau

strains instigate distinct regional and cellular patterns of inclusions, and the strains can be reliably propagated in cell cultures. Tau seeds are present in the human brain Tau seeding differs from Aβ seeding in that tauopathy is readily inducible by AD brain extracts in non-transgenic (wild type) mice. In addition, recombinant tau fibrils can efficiently instigate tauopathy in tau-transgenic mice, although the potency of recombinant tau is less than that of tau that originates in brain samples. In the CSF of AD patients, seed-competent tau is present that can stimulate tauopathy. The seeding capability of CSF tau *in vivo*, however, has not been reported. An analysis of *in vivo* tau seeding by CSF from patients with AD could be informative.

Several experiments have collectively underscored the prion-like molecular properties of aggregated tau, but current evidence indicates that tauopathy, like Aβ-proteopathy, is not infectious in the customary sense of being easily transmissible from one organism to another. Rather, in AD, the process of tau misfolding and propagation takes place entirely within the affected organism.

Prion-like seeding and AD pathology in humans

early in the development of tauopathy, and possibly prior to the histologic appearance of hyperphosphorylated tau within neurons.

Between 1958 and 1985, approximately 30,000 children received a series of injections of cadaver-derived human growth hormone (c-hGH), in most instances to correct a deficiency in growth. To obtain sufficient hormone for treatment, human pituitary glands were collected at autopsy, pooled into large batches, homogenized, and the c-hGH chemically extracted for injection. The treatment successfully stimulated growth, but years after treatment had ceased, a small percentage of the c-hGH recipients developed CJD. Subsequent studies have confirmed that the growth hormone was contaminated with PrP-prions, which presumably originated from pituitaries inadvertently obtained from patients who had died with prion disease. In 1985, c-hGH was replaced by recombinant growth hormone (r-GH), thereby effectively eliminating the possibility that the therapeutic agent would be contaminated by prions. Figure 3 contrasts the immunoreactive deposits (brown) of aggregated Aβ (A) and hyperphosphorylated tau (B) in the posterior lobe of the pituitary gland from a patient who had died with AD. The accumulation of Aβ and tau is generally mild in the pituitary.

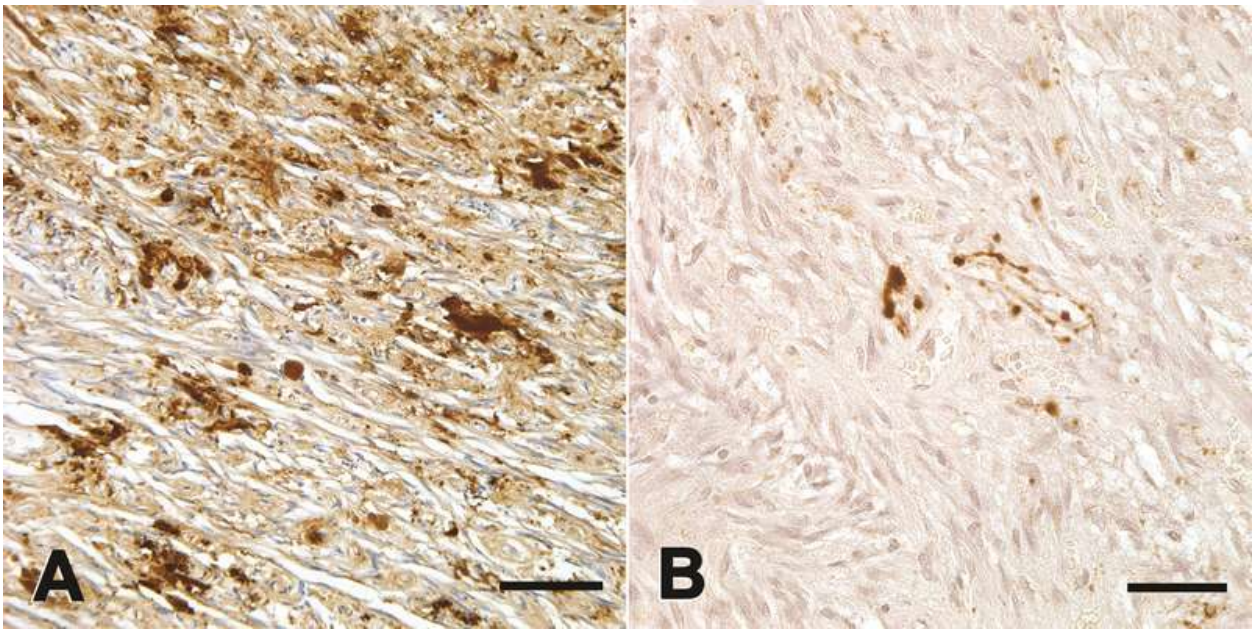

Figure 3: Contrasting aggregated Aβ and hyperphosphorylated tau in AD

Significance of the double-prion hypothesis

For researchers who support the double-prion concept, it represents a "sea change" in how the disease is understood and treated. Key implications include:

• **Focus on active prions:** It suggests that current treatments fail because they target inert protein aggregates, such as amyloid plaques, rather than the more active, misfolded prion forms that drive the disease. Developing therapies that target these active prions could be more effective.

• **Redefined markers**: Prion activity, not just the sheer number of plaques and tangles, may be a better correlate for disease progression and patient longevity. This could change how Alzheimer's is diagnosed and clinical trials are designed.

• **Unifying mechanism:** The theory provides a potential unifying mechanism for how other common neurodegenerative diseases like Parkinson's could progress, as they also involve the self-propagation of misfolded proteins.

Therapeutic implications of the prion paradigm

The seeded propagation of misfolded Aβ is an early and obligatory occurrence in the cascade of events leading to the dementia of AD, but tauopathy is a critical downstream consequence that strongly impairs brain function. Both proteins have been shown to misfold, self-assemble and convey their abnormal properties to like proteins by a prion-like molecular mechanism. Therapeutic strategies for AD stemming from the prion paradigm include:

• Impeding the production or multimerization of the proteins,

• Uncoupling the pathogenic link between abnormal Aβ and tau, and

• Promoting the elimination of the seeds from the brain.

Because Aβ-proteopathy and tauopathy each propagate by a prion-like mechanism of homologous protein corruption, it is likely that, once set in motion, the two pathologic processes advance more or less independently. If so, targeting Aβ should suffice for early prevention, but late-stage therapeutics will need to impede both branches of the cascade to be optimally effective. Another practical implication of the prion-like properties of misfolded Aβ and tau is to reinforce the importance of pristine instruments in neurosurgery. Finally, recognition of the prevalence of prionic mechanisms in neurodegenerative diseases could serve to integrate research efforts on these intractable disorders conceptually, experimentally, and therapeutically.

Linkage between Aß and tau prion activity with AD patients' longevity

Research has shown that the self-propagating prion forms of Aß and tau are most infectious in the brains of Alzheimer's patients who died at a young age from inherited, genetically driven forms of the disease, but much less prevalent in patients who died at a more advanced age. There is a remarkable exponential *decline* in the relative abundance of the prion forms of tau with age. In addition, there is an extremely strong correlation between tau prions and patients' age at death.

This research raises several questions that will need to be addressed by future studies, including:

• Whether differences in prion infectivity could explain the long-standing mystery of why Alzheimer's progresses at such different rates in different patients;
• Whether higher prion levels in brain samples from younger patients are linked to the early onset of the disease or how quickly it progressed; and
• Whether lower prion levels in older brains reflect less "infective" prion variants or instead some ability of these patients' brains to dispose of misfolded proteins.

The evidence that prion forms of Aß and tau play a specific role in AD — one that cannot be captured by simply counting amyloid plaques and tau tangles in patient brains — also raises questions on current approaches to Alzheimer's diagnosis, clinical trial design, and drug discovery.

Evidence that Alzheimer's behaves like a double prion-like disorder

The strongest evidence that Alzheimer's behaves like a "double prion (-like" disorder - involving both Aβ and tau, can be summarized as follows:

• **Both proteins show prion-like seeding and spread.** Misfolded Aβ and misfolded tau can template normal molecules to adopt the same abnormal conformation, propagate through brain networks, and drive pathology in animal models and cell systems. Reviews synthesize this across decades of work.
• **Human tissue shows measurable "seeding activity".** Biosensor cell assays detect tau and Aβ seeding in human AD samples, including at low levels—evidence of prion-like templating in patient material.
• **Clinicopathologic "network spread" matches Braak-style staging.** Imaging and postmortem studies show tau pathology advancing along functional connectivity pathways (and not purely by proximity), consistent with trans-neuronal propagation.
• **Direct quantification of Aβ and tau "prions" in AD brain.** UCSF/Prusiner-linked studies reported bioassay evidence that both Aβ and tau exist in prion-like, self-propagating forms in AD, explicitly framing AD as a "double-prion" disorder.
• **Rare iatrogenic transmission of Aβ pathology in humans.** Recipients of cadaver-derived human growth hormone (c-hGH) from the mid-20th century have shown Aβ deposition and in a 2024 Nature Medicine series, Alzheimer-like clinical/biomarker phenotypes—indicating that Aβ seeds can transmit under exceptional medical circumstances. Importantly, this does not imply everyday contagiousness.
• **What experts conclude (and caution):** The "prion principle" likely applies mechanistically to AD (seeded aggregation and spread), but AD is not considered an infectious prion disease in ordinary life; transmission, where observed, is exceedingly rare and linked to discontinued practices. Some researchers argue evidence remains insufficient to label typical AD "transmissible".

In summary, the field broadly supports that both Aβ and tau misfold, seed, and propagate in humans—hence the "double prion-like" framing—while maintaining a clear distinction from classical, routinely transmissible prion diseases.

Current views of AD as a double prion-like disorder

Over the past decade, researchers at the UCSF and elsewhere have begun to show that amyloid-beta (Aß) plaques and tau tangles from diseased brains can infect healthy brain tissue much like a prion protein (PrP}, but considerably more slowly. They were able to detect and measure specific, self-propagating prion forms of these two proteins in *post-mortem* brain tissue of 75 Alzheimer's patients. Higher levels of these prion forms in human brain samples were strongly associated with early-onset aspects of the disease and younger age at death.

Nonetheless, many scientists have been reluctant to

accept that Aß and tau are self-propagating prions — instead referring to their spread as "prion-like" — because unlike PrP prions, they were not thought to be from human brain tissue, or given transplants of the brain's protective *dura mater*, who went on to develop Aß plaques in middle age, long before they should be seen in anyone without a genetic disorder. Prusiner contends that these findings argue that both Aß and tau are prions even though they propagate more slowly than highly aggressive PrP prions.

Now, AD is currently "defined" (not caused) based on the presence of toxic protein aggregations in the brain (Aß and tau) accompanied by cognitive decline and dementia. But attempts to treat the disease by clearing out these inert proteins have been unsuccessful. [For a complete treatment of this subject, refer to Fymat (2019) and Figure 7.2.]

As stated by Prusiner on May 1, 2019: *"I believe this shows beyond a shadow of a doubt that amyloid-beta and tau are both prions, and that Alzheimer's disease is a double-prion disorder in which these two rogue proteins together destroy the brain….The fact that prion levels also appear linked to patient longevity should change how we think about the way forward for developing treatments for the disease"*. (Note that the term "double-prion disease" is not standard in neurology, but researchers sometimes use related concepts when describing AD. Figure 4 illustrates the prion forms of Aß in AD.

The new evidence that active Aß and tau prions could be driving the disease (not causing it) could lead researchers to explore new therapies that focus on prions directly. This is illustrated in Figure 4 wherein the normal form of Aß has been tagged with a yellow marker in these cells, making healthy cells a uniform pale yellow (left). Contact with prion forms of Aß — for example, in extracts from human brain tissue — forces these yellow proteins into the sticky prion form as well, leading to the formation of bright yellow clumps (right).

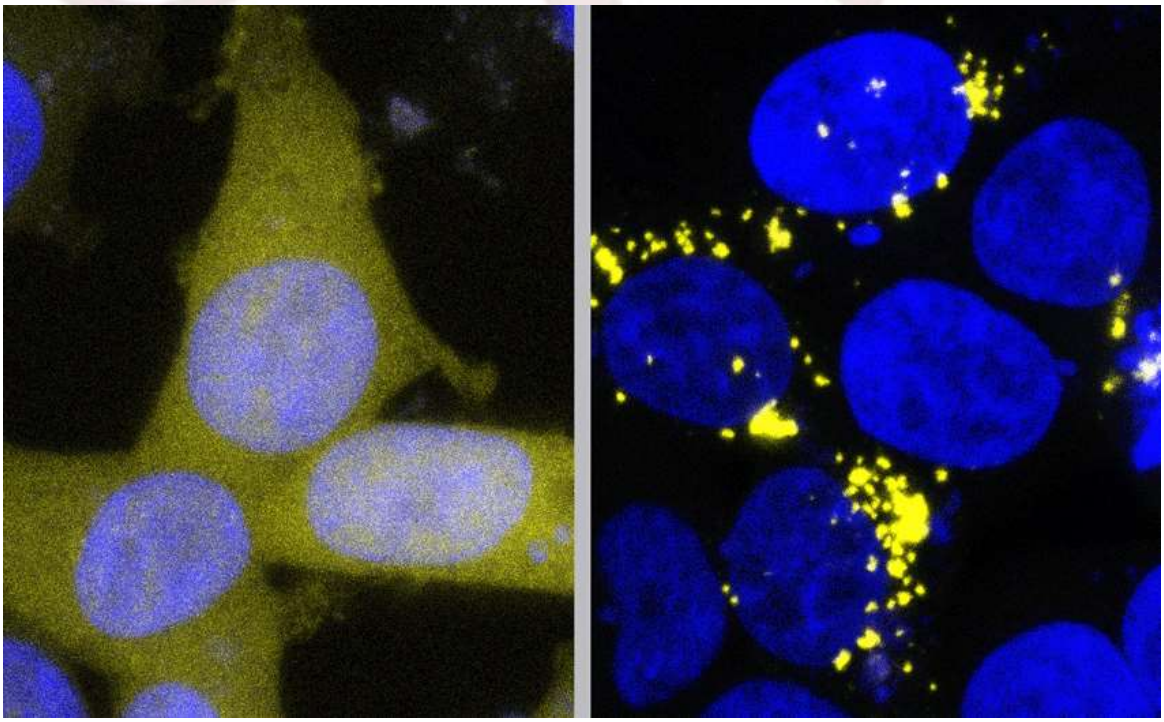

Figure 4: Illustrating prion forms of Aß in AD

Credit: Prusiner's laboratory / UCSF Institute for Neurodegenerative Diseases.

I beg to differ from Prusiner and associates. I opined earlier, and continue to opine, that AD is a run-away autoimmune disease and that Aß and tau (even if considered as prions) are but manifestations of AD, not the cause of the disease.

• The combined effect of Aβ and tau → progressive network failure → cognitive decline.
• **Importantly:** No evidence of person-to-person contagiousness in daily life.
As a result, the experts' consensus is:
• AD progression involves prion-like seeding and spread of two distinct proteins.
• The term "double-prion-like disorder" emphasizes this

Key difference from classic prion-like diseases

Alzheimer's is not contagious in the same way prion diseases are (no natural person-to-person transmission). This is the reason why the term "prion-like" is used instead of "prion disease" because the proteins share mechanisms of misfolding and spread but are not infectious under ordinary conditions. So, while Alzheimer's is not officially classified as a prion disease, some researchers do describe it as a "double prion-like disease" due to the combined roles of amyloid and tau.

The most remarkable finding may be the discovery that the self-propagating prion forms of tau and Aß are most infectious in the brains of Alzheimer's patients who died at a young age from inherited, genetically driven forms of the disease, but much less prevalent in patients who died at a more advanced age.

The above research raises a number of questions that will need to be addressed, including:

• Whether differences in prion infectivity could explain the long-standing mystery of why Alzheimer's progresses at such different rates in different patients,
• Whether higher prion levels in brain samples from younger patients are linked to the early onset of the disease or how quickly it progressed, and
• Whether lower prion levels in older brains reflect less "infective" prion variants or instead some ability of these patients' brains to dispose of misfolded proteins.

The evidence that prion forms of Aß and tau play a specific role in AD also raises questions on current approaches to Alzheimer's diagnosis, clinical trial design, and drug discovery.

Conclusions and take-aways

- Alzheimer′s disease (AD) is best understood as a dual-protein, prion-like disorder because two different proteins—β-amyloid (Aβ) and tau—misfold, self-propagate, spread through the brain in a prion-like manner, and interact and drive neurodegeneration.
- The ″double prion″ view explains why AD is progressive, network-specific, and difficult to halt once established, while remaining non-contagious under ordinary conditions.
- Unlike classical prion diseases (e.g., Creutzfeldt–Jakob disease), AD is not

contagious in everyday life, but the underlying mechanism of pathology progression shows striking parallels.

- Five pieces of evidence mitigate for the double prion concept: Misfolding and seeding; human tissue seeding activity; network spread; quantification of Aβ and tau prions; and rare transmission events.
- The issue as to whether AD is a double prion-like disorder devolves from three considerations: Prion diseases (like CJD) are caused by misfolded prion proteins (PrP) that propagate by templating their abnormal structure onto normal protein; in AD, two key proteins misfold and spread in a "prion-like" manner; and both Aβ and tau show seeding and propagation properties similar to prions.
- Many scientists have been reluctant to accept that Aß and tau are self-propagating prions because, unlike PrP prions, they were not thought to be infectious except in highly controlled laboratory studies.
- Now, Alzheimer′s disease (AD) is currently ″defined″ (not caused) based on the presence of toxic protein aggregations in the brain (Aß and tau) accompanied by cognitive decline and dementia. But attempts to treat the disease by clearing out these inert proteins have been unsuccessful.
- Alzheimer′s is not contagious in the same way prion diseases are (no natural person-to-person transmission) and that is why it is described as a ″double prion-like disease″ due to the combined roles of amyloid and tau.
- The most remarkable finding may be the discovery that the self-propagating prion forms of tau and Aß are most infectious in the brains of Alzheimer′s patients who died at a young age from inherited, genetically driven forms of the disease, but much less prevalent in patients who died at a more advanced age.
- The evidence that prion forms of Aß and tau play a specific role in AD also raises questions on current approaches to Alzheimer′s diagnosis, clinical trial design, and drug discovery.
- The strongest evidence that Alzheimer′s behaves like a ″double prion(-like)″ disorder - involving both Aβ and tau, can be summarized as follows: Both proteins show prion-like seeding and spread; human tissue shows measurable ″seeding activity″; clinicopathologic "network spread" matches Braak-style staging; direct quantification of Aβ and tau "prions" in AD brain; rare iatrogenic transmission of Aβ pathology in humans; and while the "prion principle" likely applies mechanistically to AD (seeded aggregation and spread), AD is not considered an infectious prion disease in ordinary life.
- This author differs from Prusiner and others in that he has shown that AD is a run-away autoimmune disease and that Aß and tau (even if considered as prions) are but manifestations of AD, not the cause of the disease.

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