Journal of High School Science

Identifying high efficacy potential targets in Alzheimer's disease by a mechanistic comparison with prion diseases

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Submitted: April 10, 2025, Revised: version 1, August 13, 2025, version 2, August 20, 2025, version 3, October 11, 2025
Accepted: November 1, 2025

Abstract
Prion diseases and Alzheimer's disease share many similarities in seeding activity, symptomatic and pathological presentations, and mechanisms of neurodegeneration. Accordingly, it is pertinent to inquire whether Alzheimer's should be considered; and therefore treated like; a prion disease. This mental framework would likely guide many to target the seeding of Alzheimer's as a method for altering disease progression. This review cross examines both diseases to dissect the limits to their overlap and understand how these similarities can be exploited for more effective treatment. While conventional wisdom has chosen to focus on the common seeding properties in each disease, this review concludes that targeting seeding in Alzheimer's disease would not be as effective in treating it; as opposed to targeting seeding in prion diseases. Seeding in prion diseases drives conversion from the antiapoptotic cellular Prion Protein (PrPc) to toxic scrapie Prion Protein (PrPsc). While seeding of amyloid-β in Alzheimer's does not drive such analogous conversion of benign monomers to a toxic state. The seeding activity of hyperphosphorylated tau (HPT) in Alzheimer's does. This implies promise for using anti-aggregation therapies effective for PrPsc in taupathies, on HPT in Alzheimer's. However, given that this event is downstream of amyloid-β seeding and that tau can become toxic through other means, even modulating HPT seeding may not be as effective a therapeutic target in Alzheimer's, as it may be in prion diseases. The intracellular interactions of amyloid-β and HPT exploit similar pathways in triggering apoptosis as in PrPsc. Thus, therapeutics that target these common pathways would be effective in both diseases. Additionally, while PrPc has been shown to contribute to amyloid-β toxicity, this review suggests that blocking the binding between the two proteins via allosteric or competitive inhibitors, rather than completely eradicating PrPc, would be the most optimal treatment. Such a therapy could also be applied to PrPc/PrPsc binding in prion diseases. Such a change in the thinking framework could significantly increase druggable targets for both prion and Alzheimer's therapeutics. This could also expand the relevancy of niche fields of study, like mitochondrial dynamics, from application to a singular disease, to multiple diseases.

Keywords
Alzheimer's disease, Prion diseases, Taupathies, Amyloid-β, Hyperphosphorylated tau, Seeding, Neurofibrillary tangles, Neurodegeneration, Druggable targets, Neuroinflammation

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https://doi.org/10.64336/001c.146596

Introduction

Prion diseases, as coined by Dr. Stanley Prusiner, are a group of rare and rapidly fatal neurodegenerative diseases caused by an infectious protein, or a "prion". Prion diseases lead to rapid loss of memory and cognitive function, along with falls and changes in movement. Alzheimer's Disease is also a neurodegenerative disease which leads to loss of memory and cognitive function, though Alzheimer's disease is caused by two proteins, amyloid-β and tau. Since the diseases share some similarities in the aggregation and spread of abnormal proteins in the brain, scientists have used overlaps in these two diseases to increase the understanding of each disease. This review compiles information about each disease individually and their overlaps and contrasts, as well as how prion research has changed the understanding and diagnosis of Alzheimer's Disease.

Discussion

Clinical manifestation and prognosis

Prion diseases progress quickly, from mild cognitive symptoms such as short term memory loss to rapidly progressive dementia, myoclonus, and eventually death, often within 1 year of diagnosis (1). Prion diseases encompass multiple different diseases caused by the prion protein, including Creutzfeldt-Jakob Disease, Gerstmann-Sträussler-Scheinker Syndrome, and Fatal Familial Insomnia (2). Fatal Familial Insomnia and Gerstmann–Sträussler–Scheinker syndrome, manifest with different initial symptoms such as progressive insomnia or parkinsonism (3-5). Since prion diseases present similar symptoms to other neurodegenerative diseases, extensive diagnostic tests must be performed to both rule out more treatable causes of illness and to fully diagnose the disease as being prion causative (6). Diffusion weighted imaging and fluid attenuated inversion recovery magnetic resonance imaging (MRI) help doctors visualize atrophy of the brain and identify signal abnormalities consistent with prion disease (1,6). Cerebrospinal fluid samples are usually taken to test for biomarkers of neurodegeneration, such as 14-3-3 protein and total tau, and to test for the presence of the abnormal prion protein found in prion disease using Real Time Quaking Induced Conversion (RT-QuIC) tests (1, 7, 8). There are no current therapeutic interventions available that can alter the disease course of prion diseases; although multiple clinical trials are underway for prospective future treatments (6, 9, 10).

Similar to prion disease patients, those with Alzheimer's disease experience a range of symptoms, particularly early in the disease course, but most cases involve short term memory impairment, language impairment, and progressive dementia (6, 11). Unlike prion diseases, Alzheimer's disease often spans multiple years with the growth of intraneural tau aggregates following the Braak hypothesis of pathological progression (12, 13). Since Alzheimer's shares many common symptoms with other neurological diseases, a plethora of clinical tests must be performed to both rule out more treatable conditions and to confirm a diagnosis of Alzheimer's disease (6). While MRIs that show atrophy of the hippocampus and diffusion tensor imaging MRIs that show evidence of lesions suggest Alzheimer's type pathology, these diagnostic scans are not confirmatory by themselves (6, 14). Cerebrospinal fluid and blood tests are used to both check for other causes of neurological

dysfunction, such as a vitamin B12 deficiency, and to identify biomarkers of neuronal damage and brain amyloid, such as decreased amyloid-β 42, elevated total tau and hyperphosphorylated tau (6, 14,15). However, definite Alzheimer's disease is only diagnosable via a brain autopsy performed after death (14). Alzheimer's disease is fatal, but there are treatments which may treat the symptoms or slow the disease progression (11).

Cholinergic neurons, or neurons which produce the neurotransmitter acetylcholine, are some of the first to atrophy in Alzheimer's. Consequently, there is less acetylcholine being produced in the brain as the disease progresses (11, 16) . Cholinesterase enzyme inhibitors prevent the proteolysis of acetylcholine, preserving the supply of the neurotransmitter for longer and preventing further neuronal death from a lack of stimulation from neurotransmitters (14). Additionally, NMDA antagonists used in Alzheimer's disease prevent NMDA receptors from being overstimulated and allowing too many calcium ions into a neuron, which triggers excitotoxicity and neuronal death (11, 14). The only potentially disease modifying treatments for Alzheimer's disease were recently approved by the US Food and Drug Administration in 2023 and target aggregated forms of amyloid to remove them from the brain (5). Note that in the context of comparison with taupathies – as outlined in this review - these approved treatments are not estimated to be effective; as indeed; their approval was implicitly contingent on definition and effectiveness constrained factors; as well as the lack of any approved therapies even after decades of chasing the amyloid-β hypothesis.

Pathology

Prion disease develops in one of three different ways: sporadically, genetically, or acquired (1, 15). Sporadic prion disease, the most common development trajectory, occurs when a misfolded prion protein bypasses protein quality control systems by chance, then continues to propagate and seed other prion proteins to misfold (2, 17). Genetic prion diseases, the second most common way of disease development, occur when mutations to the prion gene (*PRNP*) predispose the prion protein to misfolding (2, 4). These mutations are inherited in an autosomal dominant fashion (3, 18). Acquired prion diseases involve prions transferring from one organism to another, which can occur through consumption or through surgeries involving contaminated transplants or tools (2, 17, 19, 20). When material infected with prions is consumed, the prions may compromise the gastrointestinal tract and collect in the lymph nodes, where they start to propagate (1, 21). These prions eventually make their way through the peripheral nervous system into the central nervous system and into the brain (1). In past experiences of acquired prion disease outbreaks, such as the variant Creutzfeldt-Jakob Disease outbreak in the UK in 1996, prions in humans do not seem to have a very high transmissibility rate or have a very long incubation time given that many people were exposed but only a relatively few cases of prion disease developed (1, 19). However, prions are highly transmissible in animals and different strains and mutations mainly stem from organism to organism 'hopping' of prions in animals (2).

Since prions are transmissible, slow acting, and emergent with different 'strains', many have proposed the idea that Dr. Stanley Prusiner's

hypothesis; that of a causative misfolded protein; is not accurate – rather, a slow moving virus or virino has been envisaged to be the causative agent - with the Prion Protein (PrP) simply acting as the facilitator (22). Multiple lines of evidence have been published in support of this virino prion hypothesis, including analysis and samples of the disease driving agent of prion disease not containing any nucleic acid, and literature reviews and analyses discussing the origins of prion diseases originating from the early peptide evolution (19). Moreover, the prion hypothesis is being investigated to determine if it satisfies Koch's postulates (the original disease has to be reproduced – being grown and reproduced *in vitro* after being obtained by an infected donor, then put into a recipient) (22). This has met with some skepticism, in its attempts to fulfill Koch's postulates, given that the closest example in mammals is prion disease being reproduced in transgenic mice that were producing 16x the normal level of PrPc (Cellular Prion Protein; non-pathogenic normal form) (23). However, Koch's postulates have been proven with yeast prions and - using Protein Misfolding Cyclic Amplification - there have been promising results almost completely fulfilling Koch's postulates (23). The virino prion hypothesis is not the first and probably will not be the last hypothesis to be questioned, and for good reason as such questioning drives innovation and discovery. However, since this hypothesis has not yet been falsified, it is reasonable to accept it as being a disease driver.

Alzheimer's Disease can also develop sporadically and genetically (11). Sporadic formation of Alzheimer's pathology occurs when the amyloid precursor protein randomly goes through the amyloidogenic pathway of proteolysis and enough pro-aggregation amyloid-β monomers ($A\beta_{mono}$) are produced that can drive the progression of Alzheimer's pathology (7, 12, 15) . The risk of developing abnormal amyloid-β aggregates ($A\beta_{agg}$) can be increased in individuals with certain gene variants, such as ApoE4. Genetic Alzheimer's occurs when there are mutations to genes coding PSEN1, PSEN2, or APP, which cause a higher rate of production of pro-aggregation $A\beta_{mono}$, thereby advancing Alzheimer's pathology (7, 11). In both genetic and sporadic cases, an excess of pro-aggregation $A\beta_{mono}$ contributes to the risk and progression rate of the disease pathology (11).

Protein structure and seeding

Prion diseases are neurodegenerative diseases caused by the misfolding of normal cellular Prion Protein (PrPc) into its aberrant aggregated form, named PrPsc after the sheep prion disease scrapie (1). PrPc is a glycoprotein, attached to the cell membrane through a glycosyl phosphatidylinositol anchor, and is theorized to function in mediating cell signals to the neuron (2, 20). This theory is supported by both its location on the cell membrane and the high density of PrPc found in synaptic membranes (24). PrPc is also thought to generally be anti-apoptotic, or a protein that helps to prevent cell death (20). Normal PrP has an alpha-helix saturated protein structure, and is both protease sensitive and detergent soluble (20, 25) . Abnormal PrP instead folds into a beta-sheet saturated protein structure (1, 25). This abnormal structure has the ability to catalyze the misfolding and aggregation outside the cell of normal PrPc into more PrPsc through a process called seeding (2, 19). PrPsc aggregates and

monomers then lead to neurodegeneration (1, 25, 26) (Figure 1). It is important to note that the actual process of seeding and aggregation is what converts benign PrPc monomers into neurodegenerative PrPsc. Thus, the process of aggregation itself plays an active role in creating disease driving agents, even if the aggregates sometimes break down into monomers before inciting neurodegeneration. There are multiple ways for a PrPc to misfold into a beta-sheet saturated structure, which gives rise to different strains of PrPsc (20, 25). Many, but not all, of these strains are protease resistant, insoluble in detergent, or both, rendering protein quality control systems — meant to break down abnormal proteins— ineffective and allowing the PrPsc to continue causing damage in the brain (2).

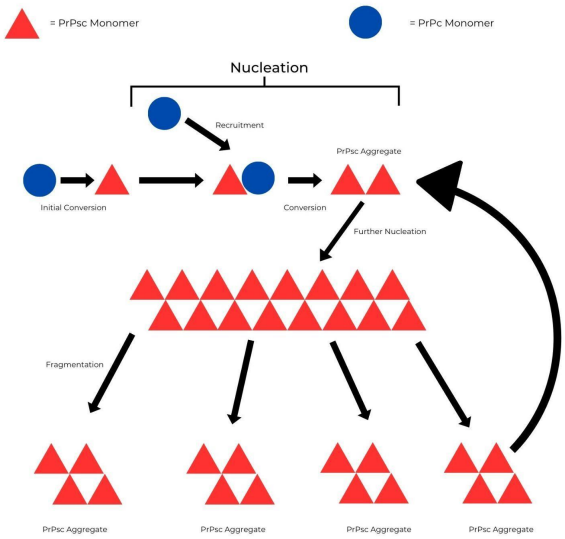

Figure 1. PrPsc aggregation starts with a PrPc monomer, which misfolds into a PrPsc monomer spontaneously or because of contact with an outside source of PrPsc, such as beef infected with Bovine Spongiform Encephalopathy. The PrPsc monomer then executes a cycle of recruiting a benign PrPc monomer, converting it into another PrPsc monomer, and adding it to the aggregate. This cycle is called nucleation, and continues until the built up PrPsc aggregate is large enough to fragment into multiple smaller PrPsc aggregates. Each of these aggregates then continue a cycle of nucleation and are able to seed the conversion of PrPc monomers to PrPsc aggregates on a larger scale.

Conversely, Alzheimer's Disease is caused by two separate proteins: amyloid-β and hyperphosphorylated tau (11). When amyloid precursor protein – a transmembrane protein – undergoes proteolysis, there are two pathways in which it can be processed. In the non-amyloidogenic pathway, amyloid precursor protein is cleaved by α-secretase and γ-secretase enzymes at their respective cleavage sites, resulting in soluble monomers that can be broken down by the cell (27). In the amyloidogenic pathway, amyloid precursor protein is cleaved by β-amyloid cleavage enzyme 1 and γ-secretase at their respective cleavage sites, which creates specific types of $A\beta_{mono}$ which, like PrPsc, have the ability to

form aggregates outside the cell (28) (Figure 2). Similar to PrPsc, both $A\beta_{mono}$ and $A\beta_{agg}$ can incite neurodegeneration (29). However, the process of aggregation does not convert any monomers into disease-driving ones in Alzheimer's; contrary to what happens with PrPc/PrPsc. Thus, it is important to note that the role of aggregation of amyloid-β is less contributory to driving disease in Alzheimer's than the aggregation of PrPc in prion diseases, since aggregation of $A\beta_{mono}$ in Alzheimer's is not always required to yield disease driving agents (Figure 3).

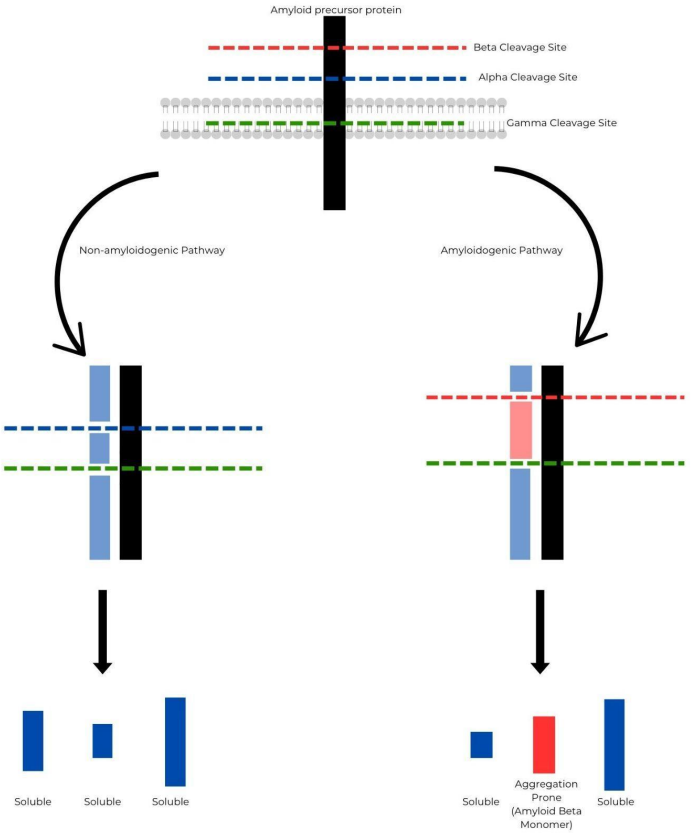

Figure 2. Amyloid precursor protein is a transmembrane protein which can be processed in two different ways. In most non-diseased brains, amyloid precursor protein follows the non-amyloidogenic pathway, in which it is cleaved by two enzymes: an α-amyloid and a γ-amyloid cleaving enzyme. These enzymes cleave the protein into soluble products that can be further broken down. However, in some instances, the amyloid precursor protein follows the amyloidogenic pathway, in which it is cleaved by a β-amyloid and a γ-amyloid cleaving enzyme. These enzymes cleave the amyloid precursor protein into soluble products (in blue) and aggregation prone products (red), the latter progresses to an $A\beta_{mono}$. When this monomer ($A\beta_{mono}$) aggregates to form the insoluble ($A\beta_{agg}$) , it cannot be further proteolyzed and can contribute to neurodegeneration.

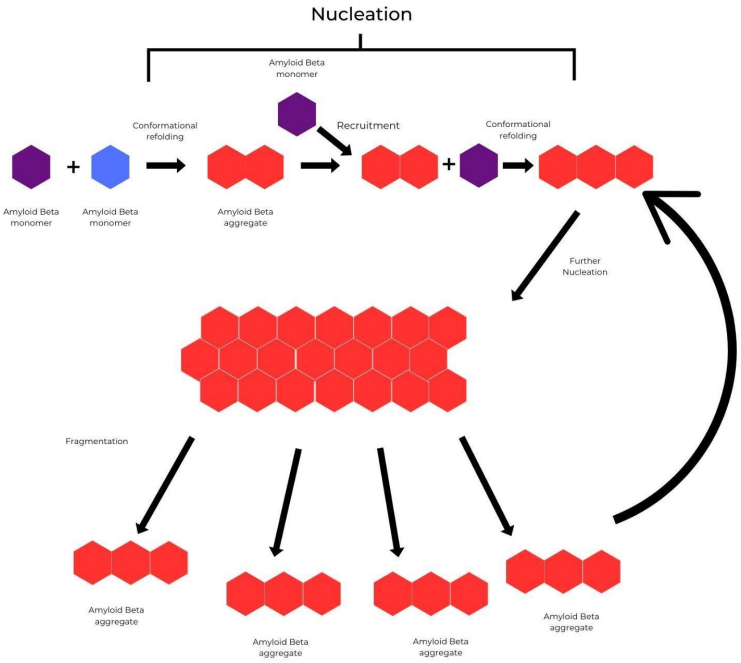

Figure 3. Amyloid Beta Aggregation. When two $A\beta_{mono}$ interact, they unfold and refold themselves to form an aggregate that is saturated in beta sheets. This aggregate; $A\beta_{agg}$; then grows via a nucleation cycle consisting of recruiting a lone $A\beta_{mono}$, and inciting conformational unfolding and refolding of the newly recruited monomer to fit the aggregate. This cycle of nucleation continues until the $A\beta_{agg}$ gets large enough to be able to be fragmented into viable smaller aggregates, each also capable of nucleation. These smaller aggregates then continue to grow and follow the same pattern of nucleation and fragmentation, causing $A\beta_{agg}$ to spread on a larger scale.

Tau, in its non-hyperphosphorylated form, is found in the microtubules of the axon and functions in stabilizing the microtubules to aid axonal transport (30). In Alzheimer's, $A\beta_{mono}$ can signal indirectly through protein kinases such as GSK3β, JNK, and ERK kinases, activating them and causing them to hyperphosphorylate tau (10, 24). The hyperphosphorylated tau monomers (HPT_{mono}) then detach from the microtubules, and create aggregates (HPT_{agg}) which can spread throughout the cell and disrupt normal cell function (7, 24). Additionally, HPT_{mono} and HPT_{agg} have been shown *in vitro* to possess the ability to convert benign normal tau into cytotoxic tau (9). They recruit the benign tau into the aggregate and cause a conformational change in the benign tau to make it cytotoxic, growing the aggregate and giving the now cytotoxic tau the ability to seed more recruitment, conversion; and thus decrease cell viability (9) (Figure 4).

This process is much more similar to the seeding process of PrPsc, since the recruitment and aggregation of HPT_{mono} to HPT_{agg} creates more disease driving agents from benign proteins, as opposed to $A\beta_{mono}$ to $A\beta_{agg}$ not creating any more disease drivers but; rather; bringing the existing ones together in an aggregate. This process has only been proven definitively to occur *in vitro*, and more studies are needed to determine whether this process happens *in vivo* as well.

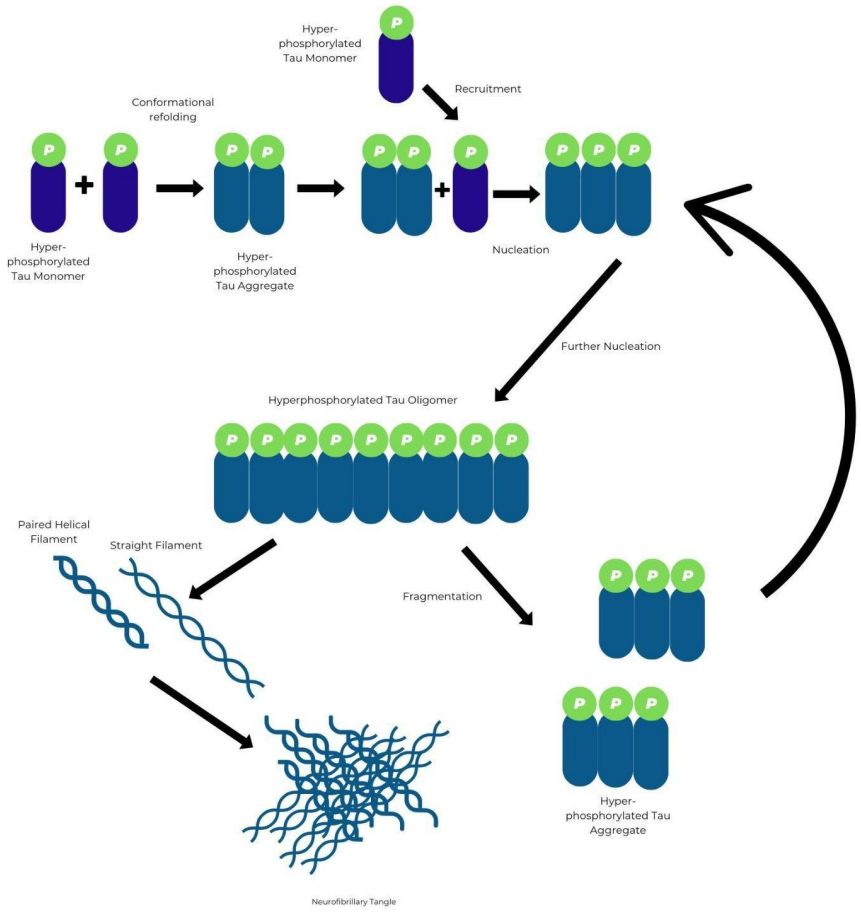

Figure 4. Tau aggregation. Hyperphosphorylated tau monomers (HPT_{mono}) join together to form aggregates (HPT_{agg}) by partially unfolding and refolding to form a dimer. This dimer will grow in size by recruiting a HPT_{mono}, which is benign on its own, and will add it to the aggregate by triggering a conformational refolding in the new recruit to fit the aggregate. Eventually, a large oligomer of hyperphosphorylated tau will either fragment completely into smaller aggregates, which feed back into the cycle of aggregation to further nucleate, or will develop into neuropril threads, specifically straight filaments or paired helical filaments. These filaments eventually come together to form neurofibrillary tangles. Paired helical filaments are more common and prevalent in the neurofibrillary tangles, and are made of two protein filaments twisting around each other in a double helical fashion, and form modulating widths of 8 nm and 20 nm. Straight filaments are not twisted around each other, and have a consistent width.

Mechanisms of neurodegeneration

Both Alzheimer's Disease and prion diseases, being neurodegenerative, cause neuronal loss. However, the exact mechanisms of neurodegeneration for either disease are not conclusively known. Many theories on how neurodegeneration occurs in both diseases focus on extracellular aggregation. The most common theory for prion related neurodegeneration is that PrPsc aggregation triggers inflammation in the brain, activating microglia (31). The microglia then release cytokines, which bind to receptors on the cell membrane and trigger an increased production of Reactive Oxygen

Species (ROS) which cause more damage to the cell and trigger apoptosis, a programmed self-killing of a cell when it is no longer functional (31). Loss of normal PrPc function or corruption of this function by PrPsc has also been implicated in some theories, where the cell loses the normal anti-apoptotic signal from the PrPc and potentially gains a pro-apoptotic signal from PrPsc, thus killing the neuron (20). Given the high density of PrPc and PrPsc in synapses, many theories propose PrPsc aggregation causes synapse dysfunction and attenuates the efficacy of synaptic pathways, preventing the neuron from receiving signals, thus either triggering the loss of neuronal signals or cell death (20). Furthermore, PrPsc in diseased brains has been shown to deposit in the white matter and other areas of the brain not typically expressing the PrP, implying that PrPsc propagates through the brain via transportation in addition to conversion of local PrPc (32). The presence of PrPsc in white matter raises the possibility that PrPsc uses axonal transport pathways between and through regions of the brain (32). PrPsc has also been proposed to travel through the brain inside the microglia after being engulfed by this immune cell (2).

While extracellular aggregation is an important source of neurodegeneration, PrPsc may also drive apoptosis through intracellular interactions, both in monomeric forms and as aggregates (33). PrPsc is theorized to cause stress in the endoplasmic reticulum (ER) when it is endocytosed and transported to the ER to be broken down by the cell, but is accumulated instead; unable to be broken down by ER enzymes because it is often protease resistant and detergent-insoluble (33). This accumulation can cause the ER to signal for cell apoptosis, which often includes activating caspases such as the ER-resident Caspase 12, which trigger the caspase cascade to cause apoptosis (33). Furthermore, ER stress can cause the lumen's calcium to leak out of calcium channels in the ER, flooding the cytosol with calcium (33). This increased cytosol calcium concentration may overactivate enzymes that are calcium regulated, which; in turn; can cause excessive degradation of proteins, membranes, and DNA (34). For example, the antiapoptotic enzyme AMP-activated protein kinase (AMPK) is activated when Calcium/calmodulin-dependent protein kinase kinase (CaMKK) phosphorylates it at specific locations, and inactivates proteins when there is a decrease in ATP to help conserve energy in the cell (34). CaMKK is often overstimulated when there is too much calcium in the cytosol, which actually drives it to overphosphorylate AMPK, inhibiting its activity and further contributing to excessive energy usage and eventual apoptosis (34). Calpains, similar to caspases, also drive apoptosis and are activated by calcium (35). The spike in cytosolic calcium drives them to initiate signaling cascades to start apoptosis (35). Furthermore, excessive calcium in the cytosol is usually taken up by the mitochondria (35). However, when the mitochondria are forced to take up too much calcium, the mitochondrial membrane potential is reduced, which decreases ATP production, and causes increased mitochondrial permeability, thereby releasing an apoptosis signaling molecule termed cytochrome c (35). PrPsc is also theorized to bind to Bcl-2 (a cytosolic anti-apoptotic protein) and cause it to be downregulated, thus impeding its anti-apoptotic property.

Similar to the aforementioned mechanisms of prion related neurodegeneration, the most common theories for Alzheimer's related neurodegeneration center around the aggregates blocking or changing cell signaling pathways. The Amyloid Plaque hypothesis, one of the original theories of Alzheimer's disease mechanisms, posits that large aggregated amyloid-β plaques incite neurodegeneration by blocking cell signaling pathways, which can cause cell death (7, 12, 36). However, the lack of correlation between amyloid plaques and disease symptoms or cell death in long range histopathology studies has led many to investigate other theories of neurodegeneration (7, 12). The Amyloid Beta Oligomer hypothesis posits that soluble amyloid-β oligomers, or small aggregates of amyloid-β rather than the large aggregated amyloid-β plaques, interfere with neuronal signaling through interactions at synapses which lead to loss of synaptic function and loss of signaling into-and out-of the neuron (14, 29). This isolates the neuron and causes a lack of stimulation, which eventually is thought to lead to cell death (36). Amyloid-β has also been postulated to bind to cell death receptors on the surface, causing a cascade of caspase activation within the cell that leads to apoptosis (2). Amyloid-β has also been theorized to drive apoptosis through intracellular mechanisms, particularly by targeting the mitochondria and activating caspases (2). Amyloid-β has been shown to promote mitochondrial fission proteins such as Dynamin-related protein 1 (Drp1), and downregulate mitochondrial fusion proteins such as Mitofusin 1 and 2 (Mfn1 and Mfn2) as well as mitochondrial dynamin-like GTPase (OPA1) (37). This increases fission of mitochondria to an excessive degree, which can also lead to the increased production of destructive ROS and a decreased Mitochondrial Membrane Potential (37). This chain of events not only disrupts mitochondrial respiration, but activates PTEN-induced putative kinase 1 (Pink1), which can trigger mitophagy (37). OPA1, in addition to aiding with fusion, also prevents cytochrome c egress from the mitochondria (37). The excessive fission, mitophagy, and lack of OPA1 thus leads to excessive release of cytochrome c and the eventual activation of caspases (37). As stated earlier, amyloid-β has been found to activate JNK, which not only phosphorylates tau but has been found to downregulate the antiapoptotic protein Bcl-w, releasing the Second Mitochondria-derived Activator of Caspases (SMAC), contributing to the caspase cascade and driving cell death (38). Similar to the scrapie prion protein, amyloid-β can drive ER stress by overloading the ER and its endosomes, causing it to leak calcium into the cytosol and interfere with calcium-ion-mediated proteins (2). As in prion diseases, CaMKK is one of these proteins (39). However, instead of inhibiting AMPK, CaMKK overactivates AMPK and causes it to excessively activate mitochondrial fission factor (MFF) and Unc 51 like autophagy activating kinases 1 and 2 (ULK1 and ULK2), which contribute to excessive fission and mitophagy (39). This significant loss in mitochondria leads to energy deficiencies and can drive apoptosis (31).

Similar to amyloid-β, aggregation of hyperphosphorylated tau is also thought to interfere with neuronal signaling. Tau aggregates can block axonal transport pathways which; in turn; can impede the transport of the mitochondria and decrease energy production in many cellular organelles (9, 14). While much of

this excess calcium caused intracellular dysfunction is thought to originate from the ER, both amyloid-β and hyperphosphorylated tau aggregates are thought to lead to excitotoxicity in the brain by allowing an excessive influx of calcium, though the exact mechanisms remain unknown (14). In fact, one treatment for Alzheimer's Disease targets this excitotoxicity by blocking a type of glutamate receptors called NMDA receptors to lessen the effects of excessive Ca^{2+} input and the resulting consequential excitotoxicity (14). However, how these NMDA receptors get overstimulated as a result of amyloid-β or hyperphosphorylated tau is not known. It is hypothesized that amyloid-β may bind to NMDA receptors to form a complex that overstimulates the receptors and propagates excitotoxicity (7). However, this conjecture has not been confirmed and more investigation is needed to conclusively understand the mechanistic roles of amyloid-β and hyperphosphorylated tau in causing excitotoxicity.

Implications and perspective

It is generally acknowledged that the proteins in Alzheimer's Disease, namely amyloid-β and hyperphosphorylated tau, behave very similarly to PrPsc, both in how the proteins form aggregates and in the various ways in which they trigger apoptosis. It may be pertinent to ask the questions as to whether and how these overlaps may affect how we effectively learn about and treat Alzheimer's or prion diseases.

The most evident similarity between the diseases is in the seeding and aggregation behavior, which has already been exploited to yield common diagnostic tools for the two. RT-QuIC is a cerebrospinal fluid test used in prion diseases to test for abnormal prion protein capable of seeding in the brain (1, 8). New research has now found that RT-QuIC proves to be an accurate test for diseases with tau aggregation, such as Alzheimer's disease, even with small concentrations of abnormal tau (8). Moreover, given that Alzheimer's related tau aggregation consists of both the 3R and 4R isoforms, the test may help distinguish Alzheimer's disease from other tauopathies and neurodegenerative disorders (4). This development could lead to earlier diagnosis, consequently starting clinical interventions at an earlier stage. Patients can thus retain their cognitive function for longer.

While such a diagnostic tool represents a significant step towards delivering more effective care for both diseases, the similarities between Alzheimer's Disease and prion diseases ideally will identify undiscovered or unexpected targets, or mechanisms to make targets druggable.

It has been proposed that Alzheimer's Disease should be considered a 'double' prion disease, because amyloid-β and phosphorylated tau both fit the key criteria of prion classification (40) including [1] must be a protein with at least 2 stable forms outside of posttranslational modifications, [2] one of which has a propensity to aggregate into a multimeric form, and [3] the multimeric form "seeds", converting benign monomeric forms of the protein into the multimeric, seed-capable form.

Both amyloid-β and hyperphosphorylated tau are stable as monomers, and are able to aggregate into various multimeric forms, which further recruit monomers into the aggregation,

thus meeting some definitions of prions (19, 21). However, there are some key differences between the pathology and seeding of amyloid-β and tau versus those of prions. Firstly, amyloid-β aggregates do not possess the capability to convert any benign monomer into a disease causing agent. Amyloid-β monomers are born out of the amyloidogenic pathway of cleaving APP, not through misfolding of a benign pre-existing monomer, and possess disease driving capabilities as a monomer without ever joining an aggregation. Contrastingly, PrPc needs to come into contact with a PrPsc aggregate or monomer and become part of the aggregation in order to gain disease driving capabilities. Hyperphosphorylated tau, like amyloid-β, is primarily built out of excessive phosphorylation rather than misfolding caused by contact with an aggregate. However, it primarily drives neurodegeneration as an aggregate, by blocking axonal transport pathways, and does possess the ability to convert some benign non-hyperphosphorylated tau.

There are no known common intrinsic disordered regions between PrPsc, amyloid-β, and hyperphosphorylated tau, which leads comparisons of between the proteins to be based more on common behavior than from common amino acid sequences (10). Along these lines, PrPsc is most like hyperphosphorylated tau in the sense that they both possess the ability to convert benign monomers by adding them to a disease driving or indicating aggregate, which is why RT-QuIC is used to test for both of them (4). Thus, if there is a treatment developed for prion diseases meant to stop the disease by preventing aggregation or binding of a benign monomer to an aggregate, it should be Alzheimer cross-over applied to the tau rather than to the amyloid-β. While amyloid-β still aggregates and causes neurodegeneration as an aggregate, the literature informs that the stage of neurodegeneration is not greatly correlated to amyloid-β aggregation, hence suggesting that amyloid-β primarily drives neurodegeneration in ways not involving large scale aggregation (7). However, amyloid-β creation, aggregation, and interaction with apoptotic cascades intracellularly and extracellularly has also been proven to be upstream of tau hyperphosphorylation and aggregation (14). This posits amyloid-β as having greater value as a therapeutic target, since modulating amyloid-β activity could stop tau aggregation altogether (14). Furthermore, amyloid-β and PrPsc seem more similar to each other in terms of intracellular mechanisms – which have been showing more promise in driving neurodegeneration than previously thought (35). Thus, treatment for Alzheimer's should focus on mitigating the impact of amyloid-β, but should not apply anti-aggregation therapies used in prion diseases to this particular protein. Instead, treatments should focus on the common intracellular apoptotic mechanisms exhibited by both amyloid-β and PrPsc.

The mitochondrion has emerged as a major player in the pathogenesis of both diseases, as both amyloid-β and PrPsc were found to incite significant mitochondrial stress, excessive fission, and excessive mitophagy, which eventually trigger the caspase cascade and starve the cell of energy (1, 41). Mitochondrial dynamics, a field of study solely dedicated to the fission, fusion, and mitophagy activity of the mitochondria, has been growing in recent years in relation to Alzheimer's Disease and has yielded many possible therapeutics for

mitochondrial dysfunction (41). Antioxidants like mitoquinone mesylate have been administered to mouse cortical neurons *in vivo* to prevent oxidative stress and cell death, and have been successful in preventing oxidative stress damage by reducing the creation of reactive oxidative species (6). They also have shown success in inhibiting amyloid-β accumulation (6). Additionally, metabolic intermediates like nicotinamide roboside, an NAD^+ precursor, have been found in many ongoing trials *in vitro* to augment general mitochondrial function, aiding in respiration and ATP synthesis (6). Some trials have also experimented with lifestyle changes to aid the mitochondria's function in Alzheimer's diseased brains, such as increased physical exercise (6). Physical exercise activates pathways that signal increased mitochondrial biogenesis and mitochondrial respiration, and have shown modest success (33). Most of these trials have been focused on Alzheimer's disease, but the fact that PrPsc also incites mitochondrial distress, creation of ROS, and caspase activation means that such efforts to preserve mitochondrial function and reduce oxidative stress may be beneficial for prion diseases as well.

Both intracellular PrPsc and amyloid-β have been shown to drive an increase in intracellular calcium, which can have many detrimental effects and trigger pathways leading to apoptosis (8, 42). Both prion diseases and Alzheimer's Disease have also been linked to intracellular copper levels (42). PrPc normally binds to copper to form an antioxidant complex (46). In prion diseased brains, copper instead binds to the PrPsc fibrils, helping to stabilize the formation and enhancing the proteinase K resistance of the preformed fibrils (21). Amyloid-β, when bound with copper, has also been found to be more prone to aggregation and toxicity, even modulating the creation of ROS (42). Copper ions have been found to mediate NMDA receptors, and the dysregulation of copper homeostasis, especially near an NMDA receptor, can trigger a toxic calcium influx (21). Thus, chelating the copper in diseased brains could aid in the calcium influx, helping with cell vitality (8). Furthermore, excess calcium is often taken up by the mitochondria, which can cause the release of cytochrome c and other caspase activators (21). Thus, chelation could aid both with the calcium itself as well as with the subsequent mitochondrial dysfunction (21). Chelation trials are ongoing for Alzheimer's, and solutions to what chelation agents work and how to safely get them past the Blood Brain Barrier can be used to also treat prion diseased brains (43).

PrPc is generally considered anti-apoptotic when functioning in a non-diseased brain. However, it appears that PrPc is actually key to the toxicity of amyloid-β, and possibly hindering their relationship could suspend some of the pro-apoptotic behavior amyloid-β has (43). Amyloid-β seems to use PrPc in a similar way PrPsc does in prion diseases – binding to the transmembrane protein and subsequently corrupting it, exploiting its access to intracellular pathways to issue pro-apoptotic signals rather than the typical anti-apoptotic ones, causing neuronal cell death (43). When amyloid-β was added to samples of homogenous PRNP negative neurons, neuronal death was prevented (43). While some studies showing that synaptic death and cognitive impairment haven't been completely avoided by blocking

the PrPc/amyloid-β connection, the avoidance of neuronal cell death could massively change the progression of Alzheimer's Disease (20). As mentioned before, PrPc is generally anti-apoptotic and getting rid of it completely could lead to other unforeseen consequences – which has also been a concern in treatments for prion diseases (43). Thus, if a therapy was developed that blocked the binding site of PrPc or amyloid-β through competition or conformational structure changes, it's possible that the toxicity of amyloid-β could be greatly reduced without the risks of eradicating PrPc (21). Furthermore, since most of amyloid-β's apoptotic effects come from its interactions, applying a similar inhibitor on other proteins or messengers amyloid-β interacts with could arguably render amyloid-β to not be apoptotic anymore. Moreover, a blocker on a PrPc binding site could theoretically be applied to the PrPc/PrPsc binding site to reduce conversion and apoptosis rates in prion diseases.

Many laboratories have attempted to create vaccines for Alzheimer's Disease and prion diseases (21). Given that prion diseases are transmissible between animals, evidenced by Bovine Spongiform Encephalitis, Chronic Wasting Disease, and Transmissible Mink Encephalopathy; as well as in humans, as in variant and iatrogenic Creutzfeld Jakob Disease, vaccines are very important to mitigating the possible spread of such a disastrous disease (26). There has been one occurrence of Alzheimer's being transmitted from person-to-person, which was through contaminated samples of cadaveric human growth hormone containing both prion and amyloid-β seeds (26). However, Alzheimer's is still not considered to be infectious, since this is the only occurrence ever recorded of transmitted Alzheimer's, and there is still no conclusive evidence to definitively state that the amyloid-β seeds from the human growth hormone were the sole and only cause of the future Alzheimer's – especially given how amyloid-β seeding has been questioned in relation to neurodegeneration compared to amyloid-β oligomers or monomers (25). Moreover, prion diseases have a higher propensity for developing into a highly contagious disease for humans as the animal strains are highly contagious between organisms, and the more transmissibility there is - the greater amount of mutations there may be - increasing the likelihood one of these strains mutating into a human - infective one (21). The high potential of prion diseases to mutate and infect humans as they have in the past, and the rapid progression of prion diseases in humans, means that vaccines could be vital to stopping human vulnerability to mutated strains (25). The challenge of prion strains being too difficult to pinpoint and target in a vaccine has held vaccine and prion therapy production back, which highlights how important it is to contain prion disease before it has the chance to transmit and mutate to another strain (7). In the case of Alzheimer's this seems unlikely to happen given how little amyloid-β protein seeding has really been found to spur neurodegeneration that was not already manifested through other means, and that Alzheimer's only exists in humans and is less likely to mutate or jump since it does not exist naturally within animals (21). However, Alzheimer's vaccines meant to prevent amyloid-β aggregation and subsequent immune responses are being developed to aid sporadic, genetic, and iatrogenic cases (21). Alzheimer's vaccines mainly focus on tagging amyloid-β aggregates, and either clearing them through an

auto-immune reaction or using the "peripheral sink" method, attracting amyloid-β to the blood and flushing it out from there (21). These attempts had some success, but the risk of an autoimmune reaction posed too significant a risk to continue without modifying the vaccine and restarting the trials (21). For prion diseases, the vaccines instead focused on preventing the binding of PrPsc to PrPc, using recombinant PrP from prokaryotes to block the binding site on the PrPc (21). This had some success with elongating the incubation period, but the recombinant PrP did not have a high enough affinity to the PrPc, thus limiting the success (21). Furthermore, intracellular PrPsc has been found to promote neurodegeneration, and the risk of the immunogen or adjuvant causing toxicity meant that the vaccines had to be redesigned with such risks in mind (44). While there have not been further development in vaccines for either disease yet, the common problems of choosing the correct adjuvant to calibrate the immune reaction or working with known toxic immunogens means that there will be overlaps in their solutions.

Given that both Alzheimer's Disease and prion diseases cause extensive neuroinflammation, there have been clinical trials using NSAIDs. When tested on prion diseased brain cells, the overall findings were that the NSAIDs were ineffective to mitigate the neurodegeneration from microglial damage, and the few cases microglial activity was lessened, actually led to more neurodegeneration from the now-more number of nonengulfed prions (44). Such results *in vitro* have dissuaded *in vivo* studies on NSAID usage for prion diseases. NSAIDs in the treatment of Alzheimer's Disease have yielded mixed results. Some studies have reported that general prolonged exposure to NSAIDs lessened the risk of developing Alzheimer's or decreased its progression (45). Some studies reported that NSAIDs were ineffective (46). When it comes to Alzheimer's, the prolonged progression time of the disease serves as something of an advantage, as the longer NSAIDs are used before and during treatment, the more beneficial they are to lessening risk of developing Alzheimer's or of developing extensive neuroinflammation (46). However, with short or intermediate term usage of NSAIDs before or during Alzheimer's diagnosis/treatment, NSAIDs could actually have harmful effects on the brain's fight against neurodegeneration (46).

Anti-fibrillization therapies have also been in development for Alzheimer's Disease (21). Data in how they manipulate the chaperones involved with facilitating amyloid-β fibrillization could inform anti-fibrillization therapies for prion diseases in the future. ApoE4, a known chaperone for amyloid-β, binds hydrophobically to amyloid-β on the 12-28 amino acid sequence, which was effectively blocked by a competitive inhibitor – a synthetic peptide homologous to amyloid-β 12-28 (21). This inhibition resulted in reduced fibril formation *in vitro* (21). There are currently no confirmed chaperones for PrPsc fibrillization, but Dr. Stanley Pruisiner and others have been searching for decades for a 'Protein X' they believe acts as a chaperone for PrPsc (2). The advancements in chaperone studies in Alzheimer's Disease could help inform the efforts in finding and inhibiting this 'Protein X', which would theoretically reduce the aggregation of PrPsc and subsequent conversion of PrPc.

Conclusion

The overlap between Alzheimer's Disease and prion diseases provides a unique mechanistic disease driving lens that is not available for most other diseases. The common mechanisms not only allow for common therapies and diagnostics, but a reshaped framework and broader set of known behavior that may be applicable to both diseases. Moreover, slight differences and nuances highlight why certain therapies might not be applicable to both diseases.

In summary, the seeding mechanisms between amyloid-β and PrPsc do not seem to have enough commonalities to imply that an anti-aggregation agent that is effective for PrPsc would also be therapeutically efficacious for Alzheimer's, specifically if only applied to amyloid-β. In contrast, the common 'recruiting of benign monomers' to disease driving or indicative aggregates, that occurs both with hyperphosphorylated tau and PrPsc implies that anti-aggregation therapies might prove to be therapeutic in Alzheimer's when applied specifically to hyperphosphorylated tau. Amyloid-β, operating upstream of hyperphosphorylated tau, may instead be suitable as a therapeutic target when its ability to hyperphosphorylate tau is impeded. This – rather than inhibiting $A\beta_{mono}$ aggregation - may be of significantly greater value, and this mechanism should be prioritized (Figure 5). Indeed, therapies targeting this (and analogous) mechanism(s) are in various stages of experimental, preclinical or clinical trials (Table 1).

Table 1. Experimental strategies to prevent Aβ-induced Tau Hyperphosphorylation

Target/Approach	Mechanism of Action	Example/Agent	Stage
Inhibit GSK3β	Blocks phosphorylation of tau at multiple sites	Lithium, Tideglusib[1]	Preclinical / Clinical (mixed results)
Inhibit CDK5/p25	Prevents overactivation of CDK5	Roscovitine[2] (experimental)	Preclinical
Enhance PP2A activity	Promotes tau dephosphorylation	Sodium selenate[3], PME-1 inhibitors	Preclinical / Phase II
Block Aβ aggregation or toxicity	Reduces Aβ-triggered signaling	Aducanumab, Lecanemab (Aβ antibodies)	Clinical
Block receptor-mediated signaling	Prevents Aβ from triggering kinase cascades	Memantine[4] (NMDA blocker), α7-nAChR[5] antagonists	Clinical
Reduce oxidative stress/inflammation	Limits kinase activation	Nrf2 activators[6], anti-inflammatory agents	Preclinical

1. Clinical trial Identifiers:NCT01350362, NCT01049399
2. https://doi.org/10.1159/000485008
3. Clinical trial identifiers: ACTRN12611001200976, ACTRN12620000236998
4. Clinical trial identifiers:NCT00255086, NCT00322153,NCT00857649, NCT05063851
5. Clinical trial identifiers: NCT00948909,NCT01549834
6. Clinical trial identifiers:NCT00164749, NCT02292238 , NCT02711683

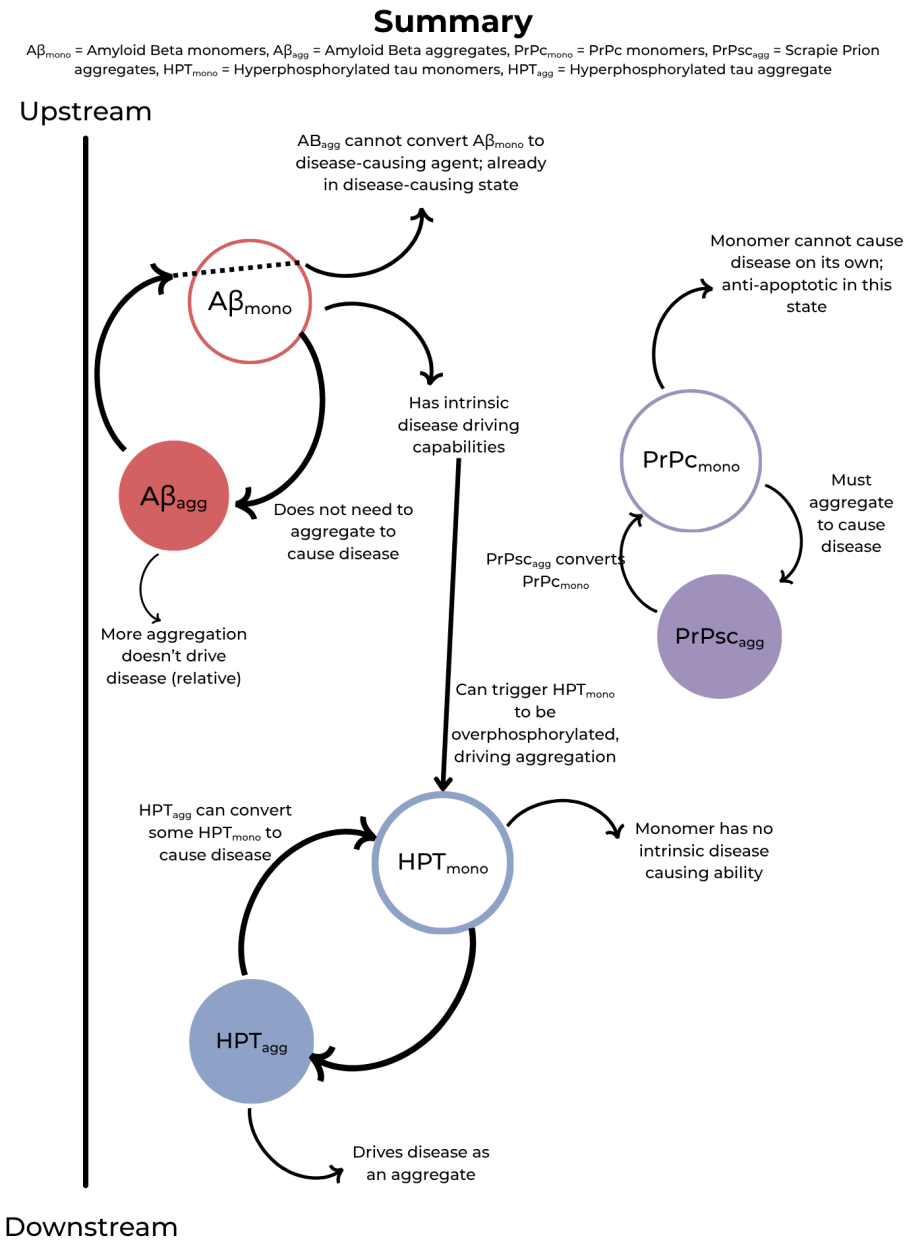

Figure 5. This figure shows a summary of the review's significant findings, namely that amyloid-β aggregation does not change the form of a monomer from benign to disease-driving but that the monomer is already in a disease-driving form, and that hyperphosphorylated tau is more similar to PrPsc in how seeding can actually convert some, though not every monomer, into a disease driving form by joining the aggregate. The events are ordered from upstream to downstream, the (left) part of the figure - Aβ and HPT - refer to Alzheimer's while the PrP_x (right) part of the figure refers to prion diseases.

In regards to PrPc's role in Alzheimer's, while many argue that eradicating PrP as a whole should be explored, blocking the binding site of PrPc or amyloid-β, via competitive or allosteric inhibitor, is likely to reduce the toxicity of amyloid-β without the risks of eradicating the generally anti-apoptotic PrPc. Moreover, this type of blocker could be applied to other binding sites which amyloid-β uses for other proteins and messengers along its pro-apoptotic tracts or binding sites between PrPc and PrPsc in prion diseases, stopping such cell death cascades from ever occurring in either Alzheimer's or prion diseases.

These similarities and overlaps between Alzheimer's and prion diseases must continue to be studied, as we still don't fully understand the molecular mechanisms of both diseases. There may be more common intermediates, molecules, and/or interaction states between them that could be exploited, given how many similar pathways toward apoptosis, aggregation or phosphorylation they use, and we can exploit targets with reasonable assurance even if they are identified in either one of the two diseases: Alzheimer's or taupathies. Their clinical and mechanistic similarities also present us with a *modus operendi* with which to investigate as-yet unexplored avenues of thought and therapeutics; instead of only relying on brute force Machine Language algorithms and Artificial Intelligence. Conversely, exploring one disease in complete isolation of the other – despite mechanistic similarities – can lead to *cul-de-sacs* and borderline acceptable clinical efficacy; partly exemplified by approved disease modifying amyloid-β plaque removal drugs. A comparison between Alzheimer's and prion diseases will set the correct course for drug targeting, discovery and repurposing (including course corrections from futile trajectories), and vindicate the power of analogy to uncover efficacious drugs.

Acknowledgements

I would like to thank Dr. Meaghan Morris for guidance, fruitful conversations on the direction and conclusions of the paper, and insightful comments on the manuscript and Dr. Abhay Moghekar for guidance on sources and the final manuscript.

References

1. Geschwind, M. D. (2015). Prion diseases. CONTINUUM Lifelong Learning in Neurology, 21, 1612–1638. https://doi.org/10.1212/con.0000000000000251

2. Colby, D. W., Prusiner, S. B. (2011). Prions. Cold Spring Harbor Perspectives in Biology, 3(1), a006833. https://doi.org/10.1101/cshperspect.a006833

3. Almer, G., Hainfellner, J. A., Brücke, T., Jellinger, K., Kleinert, R., Bayer, G., et al. (1999). Fatal familial insomnia: a new Austrian family. Brain, 122(1), 5–16. https://doi.org/10.1093/brain/122.1.5

4. Dong, T., Satoh, K. (2021). The latest research on RT-QUIC Assays—A Literature Review. Pathogens, 10(3), 305. https://doi.org/10.3390/pathogens10030305

5. Zhang, Y., Chen, J., Li, Y., Jiao, B., Luo, S. (2024). Disease-modifying therapies for Alzheimer's disease: clinical trial progress and opportunity. Ageing Research Reviews, 102595. https://doi.org/10.1016/j.arr.2024.102595

6. Ortiz, J. M. P., Swerdlow, R. H. (2019). Mitochondrial dysfunction in Alzheimer's disease: Role in pathogenesis and novel therapeutic opportunities. British Journal of Pharmacology, 176(18), 3489–3507. https://doi.org/10.1111/bph.14585

7. Kocahan, S., Doğan, Z. (2017). Mechanisms of Alzheimer's disease pathogenesis and prevention: the brain, neural pathology, N-methyl-D-aspartate receptors, TAU protein and other risk factors. Clinical Psychopharmacology and Neuroscience, 15(1), 1–8. https://doi.org/10.9758/cpn.2017.15.1.1

8. Dickson, D. W. (2004). Apoptotic mechanisms in Alzheimer neurofibrillary degeneration: cause or effect? Journal of Clinical Investigation, 114(1), 23–27. https://doi.org/10.1172/jci22317

9. Liu, M., Sui, D., Dexheimer, T., Hovde, S., Deng, X., Wang, K., et al. (2020). Hyperphosphorylation renders Tau prone to aggregate and to cause cell death. Molecular Neurobiology, 57(11), 4704–4719. https://doi.org/10.1007/s12035-020-02034-w

10. Zhou, J., Liu, B. (2013). Alzheimer's disease and Prion protein. Intractable & Rare Diseases Research. https://doi.org/10.5582/irdr.2013.v2.2.35

11. Breijyeh, Z., Karaman, R. (2020). Comprehensive review on Alzheimer's disease: Causes and treatment. Molecules, 25(24), 5789. https://doi.org/10.3390/molecules25245789

12. Braak, H., Braak, E., Bohl, J. (1993). Staging of Alzheimer-Related Cortical Destruction. European Neurology, 33(6), 403–408. https://doi.org/10.1159/000116984

13. Kellett, K. A., Hooper, N. M. (2009). Prion protein and Alzheimer disease. Prion, 3(4), 190–194. https://doi.org/10.4161/pri.3.4.9980

14. Bloom, G. S. (2014). Amyloid-B and Tau. JAMA Neurology, 71(4), 505. https://doi.org/10.1001/jamaneurol.2013.5847

15. Walker, L. C., Diamond, M. I., Duff, K. E., Hyman, B. T. (2012). Mechanisms of protein seeding in neurodegenerative diseases. JAMA Neurology, 70(3), 304. https://doi.org/10.1001/jamaneurol.2013.1453

16. Torrent, J., Vilchez-Acosta, A., Muñoz-Torrero, D., Trovaslet, M., Nachon, F., Chatonnet, A., et al. (2015). Interaction of prion protein with acetylcholinesterase: potential pathobiological implications in prion diseases. Acta Neuropathologica Communications, 3(1). https://doi.org/10.1186/s40478-015-0188-0

17. Soto, C. (2010). Prion hypothesis: the end of the controversy? Trends in Biochemical Sciences, 36(3), 151–158. https://doi.org/10.1016/j.tibs.2010.11.001

18. Zhao, M., Feng, L., Hou, S., Shen, P., Cui, L., Feng, J. (2019). Gerstmann-Sträussler-Scheinker disease: A case report. World Journal of Clinical Cases, 7(3), 389–395. https://doi.org/10.12998/wjcc.v7.i3.389

19. Jheeta, S., Chatzitheodoridis, E., Devine, K., Block, J. (2021). The Way forward for the Origin of Life: Prions and Prion-Like Molecules First Hypothesis. Life, 11(9), 872. https://doi.org/10.3390/life11090872

20. Kovacs, G. G., Budka, H. (2009). Molecular Pathology of human prion diseases. International Journal of Molecular Sciences, 10(3), 976–999. https://doi.org/10.3390/ijms10030976

21. Wisniewski, T., Sigurdsson, E. M. (2007). Therapeutic approaches for prion and Alzheimer's diseases. FEBS Journal, 274(15), 3784–3798. https://doi.org/10.1111/j.1742-4658.2007.05919.x

22. Manuelidis, L. (2006). A 25 nm virion is the likely cause of transmissible spongiform encephalopathies. Journal of Cellular Biochemistry, 100(4), 897–915. https://doi.org/10.1002/jcb.21090

23. Zou, W., Gambetti, P. (2005). From microbes to prions. Cell, 121(2), 155–157. https://doi.org/10.1016/j.cell.2005.04.002

24. Béland, M., Roucou, X. (2013). Taking advantage of physiological proteolytic processing of the prion protein for a therapeutic perspective in prion and Alzheimer diseases. Prion, 8(1), 106–110. https://doi.org/10.4161/pri.27438

25. Brown, D. R., Schmidt, B., Kretzschmar, H. A. (1996). Role of microglia and host prion protein in neurotoxicity of a prion protein fragment. Nature, 380(6572), 345–347. https://doi.org/10.1038/380345a0

26. Banerjee, G., Farmer, S. F., Hyare, H., Jaunmuktane, Z., Mead, S., Ryan, N. S., et al. (2024). Iatrogenic Alzheimer's disease in recipients of cadaveric pituitary-derived growth hormone. Nature Medicine. https://doi.org/10.1038/s41591-023-02729-2

27. Azargoonjahromi, A. (2024). The duality of amyloid-β: its role in normal and Alzheimer's disease states. Molecular Brain, 17(1). https://doi.org/10.1186/s13041-024-01118-1

28. Kellett, K. A., Hooper, N. M. (2009). Prion protein and Alzheimer disease. Prion, 3(4), 190–194. https://doi.org/10.4161/pri.3.4.9980

29. Tamagno, E., Guglielmotto, M., Monteleone, D., Manassero, G., Vasciaveo, V., Tabaton, M. (2017). The unexpected role of AB1-42 monomers in the pathogenesis of Alzheimer's disease. Journal of Alzheimer S Disease, 62(3), 1241–1245. https://doi.org/10.3233/jad-170581

30. Avila, J., Lucas, J. J., Pérez, M., Hernández, F. (2004). Role of TaU protein in both physiological and pathological conditions. Physiological Reviews, 84(2), 361–384. https://doi.org/10.1152/physrev.00024.2003

31. Li, B., Chen, M., Zhu, C. (2021). Neuroinflammation in Prion disease. International Journal of Molecular Sciences, 22(4), 2196. https://doi.org/10.3390/ijms22042196

32. Taraboulos, A., Jendroska, K., Serban, D., Yang, S. L., DeArmond, S. J., Prusiner, S. B. (1992). Regional mapping of prion proteins in brain. Proceedings of the National Academy of Sciences, 89(16), 7620–7624. https://doi.org/10.1073/pnas.89.16.7620

33. Hetz, C. (2003). Caspase-12 and endoplasmic reticulum stress mediate neurotoxicity of pathological prion protein. The EMBO Journal, 22(20), 5435–5445. https://doi.org/10.1093/emboj/cdg537

34. Moon, J., Park, S. (2020). Prion peptide-mediated calcium level alteration governs neuronal cell damage through AMPK-autophagy flux. Cell Communication and Signaling, 18(1). https://doi.org/10.1186/s12964-020-00590-1

35. O'Donovan, C. N., Tobin, D., Cotter, T. G. (2001). Prion protein fragment PRP-(106–126) induces apoptosis via mitochondrial disruption in human neuronal SH-SY5Y cells. Journal of Biological Chemistry, 276(47), 43516–43523. https://doi.org/10.1074/jbc.m103894200

36. Ashe, K. H. (2020). The biogenesis and biology of amyloid β oligomers in the brain. Alzheimer S & Dementia, 16(11), 1561–1567. https://doi.org/10.1002/alz.12084

37. Han, X., Hu, Y., Yang, Z., Jiang, L., Shi, S., Li, Y., et al. (2017). Amyloid β-42 induces neuronal apoptosis by targeting mitochondria. Molecular Medicine Reports, 16(4), 4521–4528. https://doi.org/10.3892/mmr.2017.7203

38. Yao, M., Nguyen, T. V., Pike, C. J. (2005). B-Amyloid-Induced neuronal apoptosis involves C-JuN N-Terminal Kinase-Dependent downregulation of BCL-W. Journal of Neuroscience, 25(5), 1149–1158. https://doi.org/10.1523/jneurosci.4736-04.2005

39. Lee, A., Kondapalli, C., Virga, D. M., Lewis, T. L., Koo, S. Y., Ashok, A., et al. (2022). Aβ42 oligomers trigger synaptic loss through CAMKK2-AMPK-dependent effectors coordinating mitochondrial fission and mitophagy. Nature Communications, 13(1). https://doi.org/10.1038/s41467-022-32130-5

40. Watts, J. C., Prusiner, S. B. (2017). B-Amyloid prions and the pathobiology of Alzheimer's disease. Cold Spring Harbor Perspectives in Medicine, 8(5), a023507. https://doi.org/10.1101/cshperspect.a023507

41. Hoekstra, J. G., Montine, K. S., Zhang, J., Montine, T. J. (2011). Mitochondrial therapeutics in Alzheimer's disease and Parkinson's disease. Alzheimer S Research & Therapy, 3(3), 21. https://doi.org/10.1186/alzrt83

42. Stys, P. K., You, H., Zamponi, G. W. (2012). Copper-dependent regulation of NMDA receptors by cellular prion protein: implications for neurodegenerative disorders. The Journal of Physiology, 590(6), 1357–1368. https://doi.org/10.1113/jphysiol.2011.225276

43. Kudo, W., Lee, H., Zou, W., Wang, X., Perry, G., Zhu, X., et al. (2011). Cellular prion protein is essential for oligomeric amyloid- -induced neuronal cell death. Human Molecular Genetics, 21(5), 1138–1144. https://doi.org/10.1093/hmg/ddr542

44. Veerhuis, R., Hoozemans, J. J., Janssen, I., Boshuizen, R. S., Langeveld, J. P., Eikelenboom, P. (2002). Adult human microglia secrete cytokines when exposed to neurotoxic prion protein peptide: no intermediary role for prostaglandin E2. Brain Research, 925(2), 195–203. https://doi.org/10.1016/s0006-8993(01)03273-5

45. Zhang, C., Wang, Y., Wang, D., Zhang, J., Zhang, F. (2018). NSAID Exposure and Risk of Alzheimer's Disease: An Updated Meta-Analysis From Cohort Studies. Frontiers in Aging Neuroscience, 10(83), 1–9. https://doi.org/10.3389/fnagi.2018.00083

46. Breitner, J., Haneuse, S. J., Walker, R., Dublin, S., Crane, P. K., Gray, S. L., Larson, E. B. (2009). Risk of dementia and AD with prior exposure to NSAIDs in an elderly community-based cohort. Neurology, 72(22), 1899–1905. https://doi.org/10.1212/wnl.0b013e3181a18691