

Review

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Review

Structural Variations of Prions and Prion-like Proteins Associated with Neurodegeneration

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Simple Summary: As the global life span lengthens, the likelihood of developing a neurodegenerative disease increases. Therefore, it is of great importance to develop an understanding of what causes these diseases, as well as addressing and developing effective ways to treat the diseases. This review paper addresses the prion protein and the prion-like protein found in Alzheimer's Disease in an attempt to analyze current knowledge regarding the structures of these proteins and how the variations that occur will impact disease onset and progression, as well as offer perspectives on treatments.

Abstract: Neurodegeneration is becoming one of the leading causes of death worldwide as the population expands and grows older. There is a growing desire to understand the mechanisms behind prion proteins as well as the prion-like proteins that make up neurodegenerative diseases (NDs) including Alzheimer's Disease (AD). Both amyloid β ($A\beta$) and hyperphosphorylated tau (p-tau) proteins behave in ways similar to that of the infectious form of the prion protein, PrP^{Sc} , such as aggregating, seeding, and replicating under not yet fully understood mechanisms, thus the designation of prion-like. This review aims to highlight the shared mechanisms between prion-like proteins and prion proteins in the structural variations associated with aggregation and disease development. These mechanisms are largely focusing on the dysregulation of protein homeostasis, self-replication, and protein aggregation, and how this knowledge could contribute to diagnoses and treatments for the given NDs.

Keywords: prions; neurodegeneration; Alzheimer's disease; protein homeostasis; aggregation; prion-like proteins; amyloid beta; hyperphosphorylated tau; self replication

1. Introduction

Prions are best understood as a misfolding of proteins within the brain that are not exclusive to just one species and can be transmitted between both humans and animals. The associated prion diseases are also called transmissible spongiform encephalopathies (TSEs). The term prion was coined in 1982 by Stanley B. Prusiner, as a shortened form of proteinaceous infectious particle, while studying Syrian hamsters [1]. This infectious, misfolded protein then becomes self-propagating in a not yet fully understood manner. The presence of prions always exists in animals in the forms of scrapie in sheep, chronic wasting disease (CWD) in cervids, and bovine spongiform encephalopathy (BSE) in cows being the most notable. Within humans, the most notable prion is PrP^{Sc} , which occurs when the protein PrP^C is stimulated. The presentation of prions in humans can be seen in diseases such as Kuru, all variants of Creutzfeldt–Jakob Disease (Iatrogenic, Variant, Familial, and Sporadic), Gerstmann–Straussler–Scheinker Syndrome (GSS), and both forms of Fatal Familial Insomnia (FFI) (Familial and Sporadic) [2]. However, there are differences in the pathogenesis of each of these diseases, as some may result from mutations in the *Prion Protein (Prnp)* gene, infection, or sporadic mutation.

The function of the PrP^C protein is of interest due to its possibility of helping to shed light on the prion process, with some of the processes being in the development of nervous system cells and cell signaling [3]. Also, of growing interest regarding the PrP^C protein is its ability to shift phases, and how these phase shifts may then interact with both prion-like and non-prion-like proteins.

With progress in the study of neurodegeneration, the definition of prions has evolved to be broader and widely encompassing, with the understanding that “prions are composed of host-encoded proteins that adopt alternative conformations, which are self-propagating” [4]. This broadening of what a prion is considered as effectively allows for proteins that exhibit similar behaviors to be considered prion-like, with this argument for more proteins to be considered prion-like being largely attributed to Adriano Aguzzi in 2009 due to his paper analyzing amyloid proteins' similarities to prion protein [5], with arguments being made that they should just be regarded as prions. Of significant consideration for rebranding are the two prion-like proteins, p-tau and A β , due to their presence in non-prion neurodegeneration, such as in AD. It is also worth noting that the interaction between PrP^C and the amyloid β oligomer (A β O) present in AD can trigger a phase shift in their previously established relationship [6].

Despite the progress in understanding NDs, the contribution of prions and prion-like proteins in relation to neurodegeneration continues to pose many unresolved problems. Arguably the largest issue is the understanding of the mechanism that regulates ND development and progression. This mechanism can then be broken down into three subsections: protein homeostasis (proteostasis), self-replication, and aggregation. As seen in Figure 1 below, these subsections may be interpreted as having both potential promoters (to “aid” in continued neurodegeneration) and inhibitors (to slow/prevent continuation). Therefore, this review aims to mainly summarize the recent advances of prions and prion-like proteins through structural variations, underlying regulation mechanisms, and the impact these have on disease-associated protein aggregation.

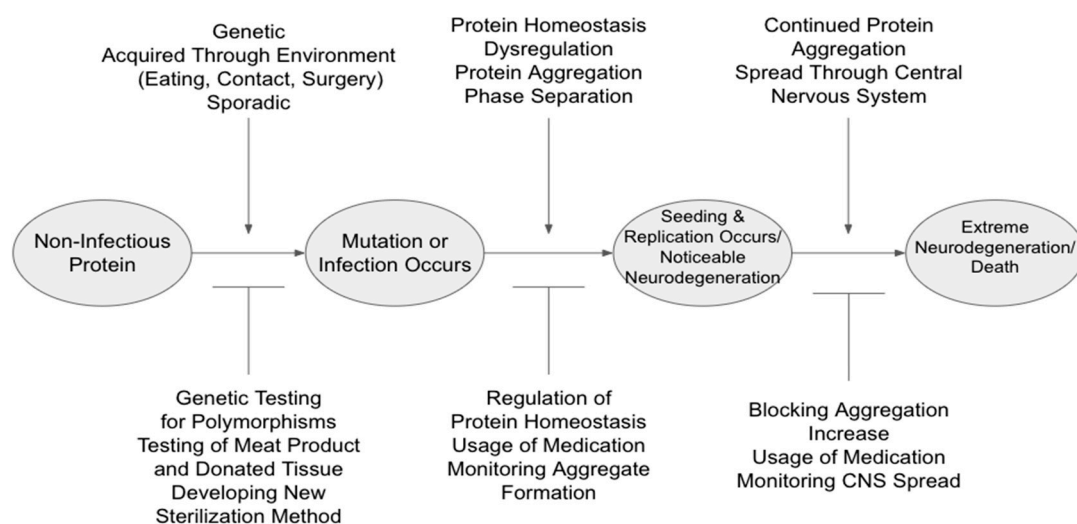


Figure 1. Simplified Roadmap of Infection Progression and Potential Promoters and Inhibitors of Infection.

2. Primary Structural Features of Prions and Prion-like Proteins

The three ND-related proteins that this review focuses on are PrP^{Sc}, A β , and p-tau. While in their biological forms, these three proteins each have their own roles that aid in maintaining neuronal homeostasis, neuronal growth, neuronal repair, stabilizing neuronal MT, and so on. The “infectious” forms become detrimental once a sizable amount has accumulated, allowing for symptoms to be observed. Recently, however, studies have begun to show that there may be interplay between astrocytes or glial cells that can be beneficial for reducing the infectious forms, while simultaneously there is a possibility that these same things may be helping spread the infectious proteins throughout the central nervous system (CNS) [7]. As of now, there are no tests that can be performed on a still-living individual that can conclusively diagnose an individual with an ND, but there are tests that can be performed that have a high level of confidence regarding the given diagnosis, such as MRI, PET, CT, SPECT, spinal tap to sample spinal fluids, and electroencephalograms [8]; however, the only

truly definitive way to diagnose NDs is post-mortem during a brain autopsy (neuropathology autopsy).

2.1. *Prnp*, *PrP^C*, and *PrP^{Sc}*

The 253 amino acids long prion protein, PrP is encoded by the *Prnp* gene, which is expressed in the brain and other tissues. The initial non-infectious structural conformation of the prion protein, PrP^C, is of alpha helices that are attached to the cell membrane at the C-terminal by glycosphosphatidylinositol (GPI) [9]. Meanwhile, the infectious form of PrP is a β sheet-rich isoform and is highly insoluble, making it difficult to do a complete structural analysis of them with current methods. There are two main hypotheses as to how the conformational change from the normal, noninfectious PrP^C form to the infectious PrP^{Sc} form occurs. The first is that the change is due to the N-terminal of the PrP^C protein, which is disordered and thus has a flexible tail. The second is the change that occurs at the C-terminal of the protein, which is speculated to be a highly ordered globular domain containing two antiparallel β -sheets and three α -helices, in contrast. These distinct differences leave room for speculation as to which terminal may be more in control of form conversion [10,11]. Furthermore, there are distinct strains of the PrP^{Sc} form, which can be categorized by histology, clinical signs, and most commonly, incubation period – where incubation period refers to the time elapsed between inoculation and onset of disease in animal models [12]. However, even though there are strains that are distinct biologically, not all can be distinguished biochemically [12].

2.2. *Prion-Like Proteins: Amyloid β and Hyperphosphorylated Tau*

The proteins present in AD-associated neurodegeneration are now deemed to be prion-like proteins. This designation results from the replication using a so-called self-template, similar to what is seen in prion proteins. The complete mechanisms behind the self-replication are still not understood, for both the prion-like proteins and prion proteins themselves, but there are many proposed mechanisms that have begun to be widely accepted.

The amyloid precursor protein (APP) is a type-I transmembrane protein whose proteolysis gives rise to amyloid β peptides. APP processing can undergo one of two pathways, one being the non-amyloidogenic pathway and the other being the amyloidogenic pathway. This second pathway contains what eventually leads to the aggregation of from flexible, soluble oligomers that cause neuropathy. Further within the realm of A β protein-related disease progression, of interest is how exactly the protein causes memory deficits alongside neurodegeneration. As such, Lesné et al, found that an extracellular 56-kDa soluble A β assembly, which was then termed A β *56 (A β star 56) is likely responsible for memory deficits by induction of transient physiological brain alterations as opposed to permanent neuropathological alterations [13].

A β can occur either sporadic or due to genetic factors. However, a recent study demonstrated that human A β entering the mice circulation can induce the occurrence of A β plaque in the brain. It is yet to be determined whether A β derived from blood can enter the brain [14]. A β pathology can be introduced to mice without human A β (hA β) by parabiosis. These mice can then develop AD-related pathologies, as well as experience phosphorylation of tau. However, what remains to be fully seen in this model is if there is a notable cognitive decline [14].

Tau, as has been mentioned, is an important factor in microtubule (MT) generation and degeneration. However, as tau undergoes phosphorylation, the tau binding to the MTs weakens until it dissociates and then will begin to aggregate together. These disordered aggregates of p-tau are known as neurofibrillary tangles (NFTs) and neuropil threads and are one of the hallmarks of AD. As tau undergoes conformation changes, the ability to undergo phosphorylation changes, along with the ability of a kinase to access a given site on the tau protein [15]. There are strong indications that the tau in AD is resistant to being dephosphorylated due to the presence of filaments within the NFTs [15].

3. Mechanistic Insights into Structural Changes Driving Protein Aggregation and Neurodegeneration

3.1. Dysregulation of Protein Homeostasis Associated with Protein Aggregation

Homeostasis of proteins (proteostasis) is becoming a critical field in ND, as the maintained regulation of protein accumulation can prove crucial for negating or increasing the likelihood of developing an ND. When the proteostasis undergoes dysregulation, the given protein system is ultimately disrupted. It is this dysregulation that then gives rise to the blockade of proteasomal/lysosomal dependent protein degradation and accumulation of aberrant proteins as there is no longer a well-maintained level of newly synthesized proteins and clearance of old or damaged proteins.

Impaired proteasomal degradation has been strongly associated with the accumulation of misfolded and aggregated proteins in neurodegenerative diseases such as Alzheimer's Disease and prion diseases [16,17]. In Alzheimer's Disease, the proteasomal system is compromised, leading to the accumulation of amyloid-beta plaques and tau tangles, which are hallmark protein aggregates [18–20]. Similarly, in prion diseases, the abnormal conversion of prion proteins into a misfolded and aggregated form overwhelms the proteasomal machinery, resulting in the accumulation of infectious prion particles [21,22]. Therefore, impaired proteasomal degradation plays a crucial role in the pathogenesis of both Alzheimer's Disease and prion diseases by contributing to the formation and persistence of protein aggregates [20].

Within proteostasis, there are many facets to consider for the clearance of overabundant proteins as well as defective proteins that can accumulate to cause pathological issues. As such, the mitochondrial quality of cells within the CNS may play a crucial role in controlling the neuropathology caused by PrP^{Sc}, A β , and p-tau, within these proteins' respective associated NDs. A recent study has found that in cells infected with Scrapie, there was an observed excessive induction of mitophagosome and mitophagolysosome formation, and the PrP^{Sc} protein was enriched in these areas, alluding to the possibility that Scrapie infection promotes mitophagy [23].

Impaired brain clearance mechanisms responsible for protein accumulation in NDs provide new diagnostic and therapeutic opportunities to delay or prevent clinical symptoms. The glymphatic system is one such, rather newly discovered, system that may be of significance in regards to the clearance of parenchymal proteins, such as A β and p-tau seen in AD. As a pathway for exchanging cerebrospinal fluid (CSF) and interstitial fluid (ISF), the glymphatic system is facilitated by aquaporin 4 (AQP4). Harrison et al. found impaired CSF-ISF exchange and AQP4 polarization in a mouse model of tauopathy. A novel AQP4 inhibitor, TGN-020, the glymphatic system disrupted glymphatic CSF-ISF exchange and tau protein clearance, suggesting that the glymphatic system could be a druggable target for AD treatment and possibly other NDs as well [24].

Liquid-liquid phase separation (LLPS) is a dynamic and reversible process that assembles biomolecular condensates as well as separates homogenous solutions into different phases: dilute and dense phases [25]. LLPS within proteins is part of a complex system that helps to control cellular functions, and abnormalities within this can lead to disease development [26]. As such, the PrP protein is not unique in the manner that it undergoes LLPS, having similar characteristics of other proteins that undergo LLPS, such as binding nucleic acids (NA) and being highly disordered [27], therefore an additional mechanism in maintaining protein homeostasis is that of protein phase separation. Understanding the conversion from the non-infectious to infectious forms of proteins is of great importance, as doing so creates pathways for potential treatments and diagnostics routes.

Thus far, the phase separations of the highly disordered PrP (and other ND-causing proteins) can be manipulated by NA aptamers to create aggregates of the bound NA:protein in similar ways to NA-free protein aggregates [27]. As protein concentration increases, the ratios of NA to protein becomes increasingly important to the likelihood of droplet formation and eventual aggregation. The addition of various NA aptamers impacts the protein structure and the ability to aggregate and maintain an aggregated state. Furthermore, there are studies showing that tau also undergoes phase separation, and can form complexes with RNA in varying salt concentrations [26]. Therefore, by

elucidating the mechanisms in which differing RNAs/NAs cause conformation changes and aggregation of prion and prion-like proteins into condensates to occur, methods to prevent aggregation may be developed by preventing phase separation dysregulation.

Based on the high affinity interaction of PrP^C with amyloid- β oligomers (A β O) and the fact that PrP^C undergoes an LLPS in which α -helical Thr becomes unfolded, Kostyley *et al.* found the interaction between PrP^C Lys residues and A β O created a hydrogel containing immobile A β O and relatively mobile PrP^C. NMR studies of hydrogel PrP^C revealed a specific α -helical conformation for natively unfolded amino-terminal Gly and Ala residues. Recombinant PrP^C could extract endogenous A β O from human Alzheimer's brain lysates into hydrogel, and a PrP^C antagonist could release A β O from endogenous brain hydrogel [4]. The findings suggest that A β species from AD can drive coupled phase and conformational transitions of PrP^C.

3.2. PTM Associated Structural Anomalies and Protein Aggregation

Alterations in primary gene and/or protein sequences or new structural domains, including peptide cleavage and mutations are essential as the structural basis of protein aggregation. Therefore, the differences in the conformation of a given protein can be the deciding factor for if an infection can fully take root in a brain. As such, all three proteins being looked at in this review are subject to structural changes that can then result in a distinct strain, depending on the causation of the structural change such as gene mutations or anomaly cleavage of proteins, among which post-translational modification (PTM) is a major contributing factor.

Accounting for impacting factors such as glycoforms within a structural model may give rise to representations of the various strains that are present within prion diseases. Since how different strains formed by the same protein elicit different clinical phenotypes remain poorly understood. Consideration of structural diversity may be the clue to understanding why these varying strains occur, based on ratios of un-, mono-, and di-glycosylated glycoforms and sialoglycoforms [28].

Regarding the PrP^C protein, differences in the glycosylation will determine the likelihood of the formation of newly generated PrP^{Sc} proteins and their associated various strains, and the ability and patterns of these proteins to deposit within the CNS [29]. Beyond just the glycosylation of the PrP^C protein being a source of new strains, patterns of carbohydrate epitopes on N-glycans, sialylation, and charge of glycans may also have an impact on strain formation and chances of occurring [30]. Tau is also subject to many different strains based on if and where it experiences phosphorylation, acetylation, and ubiquitination; which then dictates if the tau will be able to participate in AD fibrils [30].

While tau proteins occur in many different manners of phosphorylation in the brain, phosphorylation by CaM kinase is what is deemed responsible for the tau in the NFTs witnessed in AD [31]. It is not fully understood what mechanisms cause tau to become hyperphosphorylated, but one speculation is that it occurs due to an impairment of glucose levels, causing decreased tau O-GlcNAcylation which then causes hyperphosphorylation of tau that eventually leads to NFTs [32]. The NFTs that form eventually accumulate as insoluble forms. In a healthy brain, tau exists intrinsically disordered and can become ordered by having a binding partner. However, tau in an unhealthy brain is argued to be "misdisordered" and misordered, and this has been detected by the use of the antibody DC11 [33]. When DC11 is able to bind to tau, tau has taken on a new conformation, and this new confirmation-tau will then go on to form the NFTs and filaments that are seen in AD [33]. These findings demonstrate the impact of post-translational modification on the transition of structural anomaly.

3.3. Regulation of Protein Structures by Environmental Factors: Chaperones, RNA, and Ions

Present in prion diseases, as well as AD, is the development of amyloids, which eventually progresses into amyloidogenesis, as neurodegeneration progresses [34–36]. There may also be a macroenvironmental dependence that dictates the amyloid formation and infection chances of prion and prion-like proteins [37] as well as dictating the strain formation of the prion protein [38]. Continuing the focus on the environmental impact present within these proteins is also the

microenvironment in regards to the determination structure, replication, and toxicity [39]. Along with the environmental dependence, concomitant is the hydrophobicity that may be present within a species due to alterations [40]. Metal ions, such as copper, may also have a role in defining protein conformations. Depending on the region of the protein and the type of ion being considered, the protein may experience a looser or tighter conformational change, as well as affect the likelihood of susceptibility of conversion from the noninfectious form to the infectious form [41].

Chaperones of the proteins can serve to either protect from infectious form conversions, but can also be a catalyst for these infectious forms to occur depending on abundance. The different chaperones introduced to a protein may also have different efficiency rates in protection and infection, this can be seen in studies focusing on yeast prions and their varying mutability [42,43]. The presence of RNA in an environment may also impact the conformational changes that a protein may undergo. *Rai et al* found that in heterotropic conditions and when RNA is present, the proteins of interest are able to undergo transformations until they eventually form a solid-like aggregation [27]. RNA aptamers also serve as a potential way to control the conformational change or structure that may occur but there is still much to be investigated regarding the use of these aptamers regarding structural regulation.

4. Disease-Related Self-Replication and Aggregation Model

4.1. Self-Replication of Prions and Prion-Like Proteins

Over the years, in attempts to elucidate self-replication of the prion or prion-like proteins, many models have been created, but seemingly none have well fitted to the disease models perfectly. The way prion and prion-like proteins replicate is arguably a key to understanding why these aggregates occur and how to potentially treat and prevent them. The self-replication of these proteins is based on a conformational change of the protein, essentially a refolding of the native protein to a structurally changed molecule. This is seen within the PrP^C to PrP^{Sc} conversion, as the protein structure changes from being largely composed of alpha helices to largely composed of beta sheets. It has been found that self-replication leading to aggregation is a default state of disease-causing proteins [44]. The difficulty of fully understanding this remains, however, due to the differences that may result from *in vitro* versus *in vivo* studies.

The protein aggregation seen displayed in AD is of interest due to the impact of two prion-like proteins at work. The aggregation associated with the A β plaques is still yet to be fully understood, as it can occur in different structural forms, such as roughly spherical or wispy, irregular deposits [45]. The tau protein aggregated is seen as neurofibrillary tangles (NFTs), groupings of insoluble p-tau, that eventually spread throughout the brain, in a manner similar to PrP^{Sc} [5]. The spread of infectious proteins via aggregation may also be influenced by the presence of chaperones, as inhibition of chaperone proteins may enhance aggregation, while enhancement may be a potential way to prevent the spread of infectious protein aggregates in a homeostasis-maintaining manner [46,47]. Such as the chaperone proSAAS that is neuronally expressed and its function in blocking A β undergoing fibrillation [47] or the overexpression of Rnq1 being toxic to [RNQ⁺] prions toxicity, thus preventing the conversion of other proteins into amyloid species [42].

The action of aggregation replication of proteins within prion diseases and AD may also be thought of as being the default state, as it may have initially had a benefit that has yet to be evolved out of modern humans, assuming that the protein(s) in question have initially formed filamentous aggregates; as filamentous aggregate formation may be largely dependent on a secondary nucleation point, as described by Meisl *et al* in 2022 [44]. It is this secondary nucleation that causes the divide between normal growth and self-replication, as the secondary process is what allows the system to become autocatalytic and begin to grow exponentially. As seen within Figure 2, the introduction of new protein seeds on the surface of the aggregates allows for continued growth/lengthening and formation of new aggregates as time continues. As such, understanding the full function of the protein(s) role in the CNS may serve as a way to begin to focus studies in regards to preventing aggregation or preventing these secondary processes from occurring.

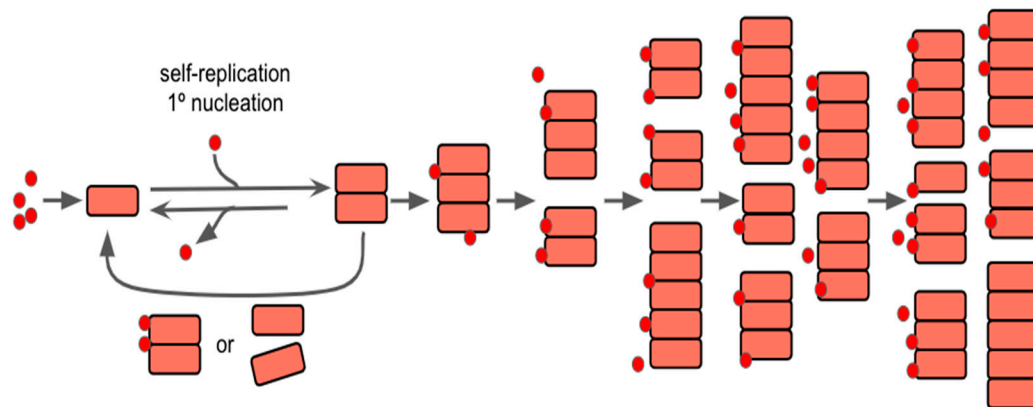


Figure 2. Self-Replication and Nucleation Model of Aggregation Reaction and Concentration Over Time. The red dots are representative of seeds for nucleation and the pink squares are showing the aggregation of proteins over time. As time progresses, seeding continually happens, and the aggregates can continue to grow in length and/or split to create new ones. Modified from [44].

4.2. Neurological Inflammation

Alongside the protein self-replication and aggregation mechanism, another factor that may influence the mechanistic progressions of NDs is that of neurological inflammation. Initially, neuroinflammation may serve a protective role within the CNS, but if it is prolonged or under dysregulation, it can change its function into that of aiding the progression of diseases [48]. There is also growing evidence that neurological inflammation may serve as a way to spread the infectious proteins throughout the CNS via astrocytes and microglia [7,49].

Of growing interest regarding neurodegeneration caused by both prion and prion-like diseases is the potential role that astrocytes may play in the spreading of these misfolded proteins. It has been noted that animals have noticeable aggregate formation in astrocytes [50], as well as the possibility of astrocytes playing a role in prion infection [51]. As animal-based prions act rather similarly in infection models, it is possible to speculate that the human astrocyte would also be playing a crucial role in both prion and prion-like infections. In a PS19 mouse model as early as 3-4 months, the microglia are activated in the brain and spine; and at 6 months old, there are reactive astrocytes in the CA3 region of the brain in a study focusing on tauopathy [52]. This hypothesis has been further studied in animal models, as well as the role of astrocytes in neuroinflammation in not only prion disease but prion-like protein diseases, such as AD. Worth noting, however, is that astrocyte-associated infection, and by extension, the microglia-associated infection, spreading may be limited to a specific type of infection, due to there being three categories: Genetic, Sporadic, and Acquired, which occur at different rates.

5. Perspectives in Prevention, Diagnosis, and Therapy

All present methods of treating NDs are aimed at halting the progression of symptoms while also trying to prevent any new symptoms from developing for as long as possible. As of now, there is no cure for any ND, but there is considerable interest in developing increasingly improved treatments until a cure can be developed.

Both pharmaceutical-based and therapeutic-based treatments have a large number of aspects to target, such as 1) the prevention of A β protein from forming, accumulating, and spreading within the CNS; 2) delaying and preventing cognitive decline from occurring and treating it when/if it does occur; 3) treating neuroinflammation and any resulting apoptosis while trying to enhance neuroprotection. Treatments targeted towards the p-tau protein need to focus on the reduction of hyperphosphorylation from occurring and a reduction of the accumulation and spread of p-tau and NFTs in the CNS; as well as similar focus as 2) and 3) in the treatment of the A β proteins. Similar to treatments for A β protein and p-tau protein, the treatments for the PrP^{Sc} protein will also need to

focus on prevention of formation, accumulation, and spread, as well as the previously listed focuses of 2) and 3), but also needs a focus on preventing infection from being able to potentially spread to other individuals and species.

5.1. Pharmaceutical-Based and Therapeutic-Based Treatment Methods

Pharmaceutical-based treatments for neurodegeneration have largely focused on immunosuppression in order to prevent the large spread and continual occurrence of misfolded proteins. Currently, a large focus of pharmaceutical treatment is focusing on researching the repurposing of already existing medication in order to speed up the development of a widespread treatment option [53].

Therapeutic treatments for neurodegeneration are largely focused on individuals that have a genetic predisposition to develop an ND. This focus aims to delay the onset of noticeable systems for as long as possible and tends to rely on pharmacological approaches in order to stave off the accumulation of the infectious proteins isoforms.

As the brain continues to be studied and systems within it are uncovered and researched, more potential treatment options for NDs become available. One such is the usage of the glymphatic system in AD in order to clear out A β and p-tau as the proteins accumulate. When the system was first described in 2012 by Maiken Nedergaard and colleagues, the dependency on astroglial cells was once again highlighted [54]. While most of the research on the glymphatic system has focused on the A β protein, such as in Peng *et al.*, there is a growing number of studies focusing on the MT-associated tau protein, such as in Harrison *et al.* [24,55].

The App^{NL-G-F/NL-G-F} mouse model developed by Sakakibara and colleagues poses the potential to serve as a good base for developing therapeutic treatments for AD-related A β plaque formations [56]. Beyond just developing new animal models with better human accuracy, there needs to be a way to trace the presence of the proteins within humans, such as developing ways to flag the proteins, such as what Hosokawa-Muto, J. *et al.* did in order to perform FRET analysis on the protein, albeit this method was used in an attempt to elucidate structural information [57].

5.2. Notable Advancements in Treatments in Recent Years

PrP^C can serve in a neuroprotective capacity when interacting with A β O in astrocyte cells to prevent oxidative damage that can eventually contribute to neurodegeneration [35]. However, PrP^C can also interact with subsets of A β O in AD to further cognitive impairment as the disease progresses [58]. Furthermore, differing biomarkers that are used in the diagnosis and monitoring of AD are also a field of increasing focus. Such as monitoring the accumulation of neurotoxic protein aggregates and the resulting neurodegeneration through blood [59] or the potential for diagnosis and monitoring disease progression through the retina [60].

As reviewed by Murakami, K. *et al.*, aptamers have become a popular topic in regard to the potential for treating amyloidogenic proteins, such as PrP^{Sc} and A β . The use of aptamers for treatment is a prosperous but difficult possibility [61]. This is due to the existence of DNA and RNA aptamers, as well as the many different options that currently exist to target a given part of a protein. CRISPR/Cas9 gene editing may also serve as a way to treat prions and prion-like proteins, especially for those with a genetic predisposition for a given disease. One study by Castle *et al.* in 2022 attempted to introduce a null Prnp allele or edited Prnp gene into mice, which while overall unsuccessful, showed promising aspects for a basis to further develop this possibility from reworking the issues that arose within the study, such as focusing on developing a complete germline [62].

Autophagy stimulation is another treatment method that has been of popular interest in regard to treating prion infection due to the ability to manipulate autophagy at different points in the infection stages. This, along with other treatments, poses difficulties due to the fear of the likelihood of prions developing resistance to treatment. As such, one group has recently tried a combination of autophagy stimulation and cellulose ethers as both are known to show positives results in regards to prion reduction, but this combination did not show as good results as compared to individual treatments leaving still more to investigate for possible combination treatments [63].

6. Conclusions

The significance of this review will lie in the improvement of understanding the mechanisms of structural changes and protein aggregation in prions and prion-like proteins that are seen in AD and the neurodegeneration associated with each respective protein. As more interest regarding prions and infectious proteins grows, the exploration of parallels and structural information will hopefully aid in developing increasingly successful treatments for preventing neurodegeneration before it starts. Along with helping to prevent continued ongoing neurodegeneration from occurring, and listing possibilities of infection occurrence in common materials, such as wood, concrete, and surgical equipment, as thus far there is no method that exists to successfully prevent transmission of prions.

Therefore, as more information regarding the structure of the infectious prion protein is achieved and understood, it will hopefully lead to better treatments for diseases associated with prions and prion-like proteins, such as AD, as explored throughout this review. Recent research on prions has begun to link novel structures and mutations, such as amino acid replacements, protein seeding, environmental changes, and hydrophobic cores, in prions and prion-like proteins to dysregulated homeostasis, leading to misfolding, propagation, and aggregation of these proteins. By summarizing recent advances in causal relations of structural anomaly and the potential of aggregation model, we disclose underlying mechanisms in the onset of neurodegeneration from the perspective of prion diseases and AD and the possible interlinking of the proteins associated with the two.

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