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REVIEW

A review on current theories and potential therapies for prion diseases

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Abstract

Prion diseases are neurodegenerative disorders that affect both humans and animals. They are commonly characterized by the absence of DNA and RNA and are distinguished from inherited or infectious forms. The cellular prion proteins (PrP^{C}) misfold and accumulate into their pathogenic isoforms in these diseases. Disease conditions like Gerstmann-Straussler-Scheinker disease, Creutzfeldt-Jakob disease, and fatal familial insomnia are all related to prion proteins. The majority of the patients with prion disorders have a life expectancy of less than a year. An effective therapeutic approach for these prion diseases remains a formidable challenge. This review focuses on novel therapeutic approaches, such as antibody-based treatments that aim to stop normal proteins from changing into the harmful form of the prion protein (PrP^{Sc}). Additionally, the review discusses the potential of RNA interference, antisense oligonucleotides, anti-aggregation compounds, β-sheet breakers, and stem cell-based therapies in addressing prion diseases.

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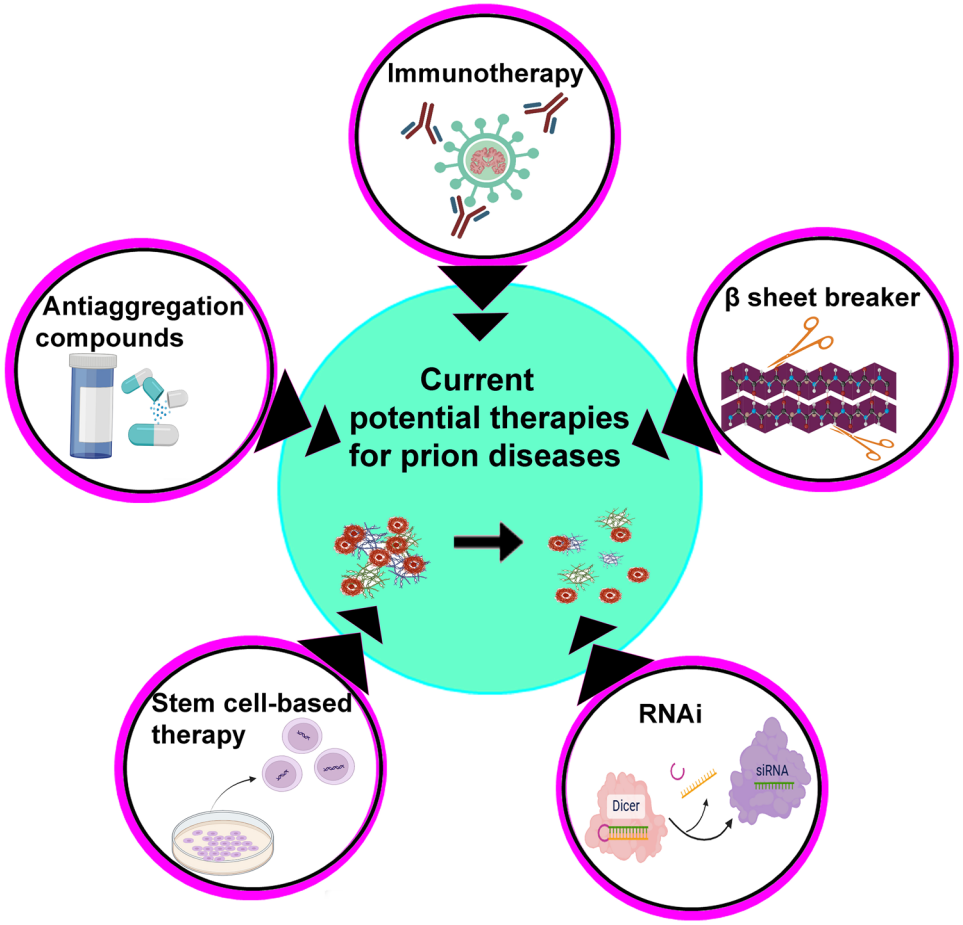
Graphical abstract



Keywords Anti-prion agents · Prion protein · Immunotherapy · Transmissible spongiform encephalopathies · Amyloid degrading agents

Abbreviations

PrP	Prion protein
sCJD	Sporadic creutzfeldt-jakob disease
CJD	Creutzfeldt-jakob disease
GSS	Gerstmann sträussler scheinker disease
GPI	Glycophosphatidylinositol
PrP^{C}	Cellular prion protein
PRNP	Prion protein gene
PrP^{Sc}	Scrapie isoform of prion protein
CTP	Cell-based therapeutic products
ZFRs	Zinc finger repressors
(ASOs)	Antisense oligonucleotides

Introduction

Protein misfolding plays a major role in several neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), and prion diseases. These conditions are collectively referred to as protein-folding diseases due to the abnormal accumulation of misfolded proteins in the brain [1] Although the exact causes are still under investigation, recent studies indicate that non-coding RNAs might affect the aggregation of amyloid proteins, including α-synuclein, in PD [2].

Prion diseases or transmissible spongiform encephalopathies (TSEs) are fatal neurodegenerative conditions that affect humans and other mammalian species (e.g., goats, cattle, minks, sheep). These diseases are instigated by the structural changes of cellular prion protein (PrP^{C}) into infectious isoforms (PrP^{Sc}) [3]. Moreover, these misfolded proteins

have a large amount of β sheets in their posttranslational conformation compared to the native protein form (typical α-helices). The native prion protein, PrP^{C}, is a 32 kDa glycosylphosphatidylinositol (GPI)-anchor protein with a carboxy-terminal, structured globular domain mainly expressed by neurons in the brain [4]. The pathological hallmark of prion disease is a spongiform appearance in the brain, characterized by nerve cell loss, gliosis, and vacuolation [5].

The term prion was first described in 1982 by Stanley B. Prusiner, and it refers to an infectious disease caused by the protein. Fundamentally, it acts as an infectious agent as it travels from cell to cell in patient's body. However, unlike bacteria or viruses, they do not contain DNA or RNA; rather, they are composed of protein. Prion diseases are classified into three forms –sporadic, genetic, and acquired. Approximately 1 in 1,000,000 people live with one of these diseases each year [6]. In humans, sporadic prion disease is the most prevalent form of prion infection. Approximately 85–90% of cases of human prion disease are caused by sporadic CJD (sCJD). Infectious causes of scrapie in sheep, chronic wasting disease in cervids, transmissible mink encephalopathy in farmed mink, and bovine spongiform encephalopathy in cattle have been identified. In addition to sporadic fatal insomnia, sporadic Creutzfeldt–Jakob disease (sCJD), and variably protease-sensitive prionopathy (rVPSP) are some rare entities [5].

Genetic prion disease consists of three distinct clinical-pathological phenotypes, such as the genetic form of CJD (gCJD) and fatal familial insomnia (FFI), which are caused by autosomal dominant mutations in the PRNP gene and Gerstmann–Straussler–Scheinker (GSS). PRNP is a 16 Kb long gene with two exons; one exon serves as a transcriptional beginning point, whereas the other exon contains the open reading frame (ORF) that codes for the 253 amino acids (PrP protein). As of now, 40 types of mutation have been reported in various forms of genetic prion diseases. [7, 8]. The most common mutations associated with gCJD, FFI, and GSS are summarized in Table 1.

Other remaining cases, like iatrogenic exposure (iatrogenic CJD [iCJD]) or ingestion (Kuru and variant CJD [vCJD]), occur via animal-to-human transmission and human-to-human transmission, respectively. Specifically, 2–4% of variant CJD is acquired by contaminated human tissues (transplants, blood transfusions, cadaveric hormone infusions) or infected foods (e.g., beef products) [9, 10].

Currently, there are no effective treatments for prion diseases, and therapeutic development remains a major challenge due to the unique replication of prions. Various therapeutic targets using chemical and biological sources have recently been developed. Here, we have discussed the recent research advancements and therapeutic strategies for prion disease. The potential therapeutic strategies targeting

Table 1 Common PRNP gene mutations in genetic prion disease

Genetic prion disease	Phenotypic features	Mutations
gCJD	Rapid dementia, myoclonus, typical CJD pathology	Gly114val
		Val180Ile
		Thr183Ala
		Thr188Lys
		Arg208His
		Ile215Val
		Val210Ile
		Glu211Gln
		Glu196Lys
		Ile215Val
FFI	Dysautonomia, thalamic degeneration, severe insomia	Asp178Asn
		Met129met
GSS	Cerebellar amyloid plaques, dementia	His187Arg
		Phe198Ser
		pro105Leu
		Pro105Thr
		Ala117Val
		Gly131Val
		Glu2011Gln
		Gln212Pro
		Gln217Arg
		Tyr226-nonsense
		Gln227-nonsense

prion include immunotherapy, antisense oligonucleotides, antiaggregation agents, PrP^C conversion, β sheet breaker, Stem cell-based therapies. An overview of these strategies is summarized in Table 2 to illustrate their significance in prion disease treatment development.

PrP^C conversion

In prion diseases, the conversion of cellular prion protein (PrP^C) into a pathogenic isoform (PrP^{Sc}) is a common event in the pathogenesis of fatal transmissible spongiform encephalopathies (TSEs) [11]. This conversion changes PrP^C, an α-helical, protease-sensitive protein, into a β-sheet protease-resistant protein [12, 13]. PrP^C is a normal cellular protein that is anchored to the outer layer of the plasma membrane through glycolipids. The conversion of normal to a pathogenic form of the protein occurs when PrP^C reaches the plasma membrane or gets incorporated through the endocytic pathway. PrP^C to PrP^{Sc} conversion is a spontaneous phenomenon that elicits prion pathogenesis [14]. The prevention of such conversion in the brain and neurons can prevent the disease's progression and degenerative changes. Several compounds have been identified to have variable degrees of effectiveness in interfering with this conversion process [15]. A list of some of these inhibitors and their mode of action is discussed in Table 3.

Immunotherapy

Immunotherapy is seen as a viable treatment option for many diseases in humans that are incurable, including neurodegenerative disorders, due to its high specificity and minimal adverse effects [26]. The first immunotherapy report on neurodegenerative disease was studied in 1999 [27]. Recently, both passive (mediated by antibodies) and active (mediated by vaccines) immunization strategies have been used in treating prion diseases. It also shows distinctive effects against prion diseases and in the clearance of misfolding. Numerous investigations using various antibodies have been conducted because the binding of PrP^C-antibodies can prevent the conversion of PrP^C to PrP^{Sc} [28]. However, the vaccine induces antibodies and, therefore, halts the spread of PrP^{Sc} and prevents the shedding of the prions responsible for chronic wasting disease (CWD) in the peripheral tissues, which is believed to be the major determinant for the effective lateral transmission of CWD in infected animals. On the other hand, uninfected animals with anti-PrP antibodies would be prevented from getting infected via peripheral routes, which is the natural pathway for CWD prion transmission [29]. Till now, three primary strategies have been used: adoptive transfer of PrP-specific CD4 + T lymphocytes, therapy with antibodies targeting PrP^{Sc}, and vaccinations with antigen-loaded dendritic cells [30, 31].

Active immunotherapy and Passive immunotherapy

Magnetic resonance imaging (MRI) has been used in Alzheimer's disease (AD) and other neurodegenerative diseases to monitor the changes in structural atrophy [32]. The amount of neurofibrillary degeneration in the brain can be decreased using active immunotherapy since it has several beneficial characteristics that make it an excellent option for this task. For example, active immunotherapy does not cause the inactivating anti-drug antibodies that bane many passive immunotherapy treatments. Ultimately, it is a viable choice for primary prevention because it is affordable, simple to use, and effective [33]. Moreover, repeated induction is not needed in active immunotherapy and is commonly used in human prion diseases. Certain pathogen-specific forms of protein and topology are determined, and these monoclonal antibodies control the prion protein growth. Three PrP^{Sc}-specific epitopes have been developed so far. They are a YYR motif in β-sheet 2, a rigid loop connecting β-sheet 2 to α-helix, and a YML motif in β-sheet. [34].

Passive immunotherapeutic approaches will be more effective than active immunization. The majority of body tissues express the endogenous cellular prion protein, which is known to be an ineffective immunogen due to its host tolerance. However, this limitation can be overcome by using PRNP knockout, which lacks PrP expression and, therefore,

Table 2 Therapeutic targets against prion amyloids

S.No	Therapeutic strategy	Mechanism of action	Target
1	PrP^C conversion	Infectious agent, prevents misfolding and conventional conformation	Inhibits PrP^C formation
2	Immunotherapy	Misfolded prion proteins can be removed or reduced by antibodies	Targets PrP^C to prevent its interaction with PrP^{Sc}
3	RNAi and antisense oligonucleotides	Suppress PrP^C to PrP^{Sc} synthesis at the mRNA level	Targets PRNP gene expression
4	Anti-aggregation compounds	Decreases and reverse the development of fibrils	Inhibits PrP^{Sc} misfolding
5	β sheet breaker	Alters the β sheet conformation in prion fibrils	β sheet structure in PrP^{Sc}
6	Stem cell-based therapy	Promotes regeneration	Targets neuronal tissue

Table 3 Drugs that can prevent the conversion of PrP^{C} to PrP^{Sc}

Sl. No	Drug Name	Outcome	References
1	Resveratrol	It increases cellular resistance to prion-related damage by promoting autophagy, blocking BAX translocation, maintaining mitochondrial function, reducing cytochrome release, and protecting neurons from PrP (106–126) induced toxicity	[16]
2	Carbazole Derivatives	The fluorescent GN8 analogue and biofunctional carbazole derivative 2b slowed the production of amyloid, and it inhibited PrP aggregation in RML-infected cells	[17]
3	Maltose poly(propyleneimine) generation five (mPPIg5) (Dendrimer)	MPPIg5 (maltose polypropylene imine) is a highly promising dendrimer with very low cytotoxicity. A study was conducted to determine whether it was effective in eliminating PrP^{Sc} from scrapie-infected neuroblastoma cells. MPPIg5 has a similar anti-prion activity to STI571 and suramin despite its low cytotoxicity	[18]
4	5,7,8-Trimethyl-3,4-Dihydro-2*H*-1,4-Benzoxazine Derivatives	In particular, 2-(4-methylphenyl)-5,7,8-trimethyl-3,4-dihydro-2H-1,4-benzoxazine showed the most significant potential to be used against prion diseases as a therapeutic agent	[19]
5	Poly-L-Lysine (PLL)	The efficacy of PLL against plasminogen in the current study. As shown in cell-free, cell culture, and mouse models of prion diseases, PLL strongly inhibited PrP^{Sc} propagation	[20]
6	Lactoferrin	It inhibited PrP accumulation and prion infectivity by partially limiting protease-resistant PrP synthesis	[21]
7	Imatinib Mesylate	Mice treated with the drug at an early stage of peripheral Scrapie infection showed a delayed onset of clinical disease and an absence of PrP^{Sc} in the central nervous system (CNS). However, no PrP^{Sc} clearance effect was observed in the CNS when the drug was administered intraperitoneally or intracerebrally	[22]
8	Nuclease-Resistant 2'-Amino-2' Deoxypyrimidine-Modified RNA Aptamers	Aptamer DP7 binds to the full-length prion proteins of humans, mice, and hamsters. In neuroblastoma cells that were persistently infected with prion, aptamer DP7 significantly reduced the percentage of de novo synthesized PK-resistant PrP^{Sc} within 16 h	[23]
9	Polydatin	The potential of polyphenolic polydatin modulated the prion protein misfolding	[24]
10	Polyornithine and polyhistidine	The anti-prion effect of Polyornithine and polyhistidine showed a significant reduction in prion protein levels in infected mice	[25]

does not exhibit tolerance to prion antigen [35]. Researchers have recently proposed monoclonal antibodies targeting PrP as a treatment for prion disease. They have shown that they can cure prion-infected cells (in vitro) and significantly delay the onset of prion disease in mice [36]. The first study of this antibody therapeutics was conducted in the mid-1980s, in which a rabbit PrP antiserum was developed against PrP27-30 suppressed prion infectivity. In the following years, various monoclonal antibodies were developed by immunizing homogenous prion knockout to target specific epitopes and determine the most effective combination of efficacy and fewer side effects [37]. According to a recent study, an intramolecular R208-H140 hydrogen bond (H-latch) was induced in PrP^{C}, which altered the flexibility of the α2–α3 and β2–α2 loops, and it also conferred that this high-affinity ligand blocks H-latch induction and protected it from prion toxicity. Therefore, preventing the H-latch formation prolonged the prion-infected mice [4]. On the other hand, the same vaccine was noticed with excellent results in a study conducted on prion-infected deer [38, 39]. A dendritic cell loaded with PrP98-127 peptides effectively delayed prion disease progression in scrapie 139A infected mice [40]. Another study revealed that the therapeutic effect of PRN100 was tested in humans for the first time using the anti-PrP^{C} monoclonal antibody ($IgG_4\kappa$ isotype; PRN100). Six patients with CJD were treated with repeated intravenous administration of PRN100. Neuropathological examination recommended that this repeated treatment could clear disease-related PrP,

while no side effects were noted [41]. The immunotherapeutic approach targeting the prion protein is depicted in Fig. 1.

RNAi

RNA interference (RNAi) treatments are currently being developed for prion diseases. Researchers have successfully extended the lives of mice infected with scrapie, a disease similar to Creutzfeldt-Jakob's disease (CJD), using gene-silencing technology [22]. Human prion diseases are far from being cured with RNAi, given that a high proportion of cells must be treated before a beneficial effect can be observed. Bovine spongiform encephalopathy (BSE) and CJD in humans are prion diseases that currently lack effective therapeutic options [40]. These diseases arise from the misfolding of normal prion proteins and their resistance to breakdown, leading to rapid, fatal brain degeneration [41]. It is possible to eliminate prions by knocking out the genes entirely, including both their normal and abnormal forms, as a potential strategy for combating the disease. The prion gene was knocked out in mice, yet they remained healthy and were protected from scrapie when inoculated with prions [40].

In scrapie-infected mice, lentivirally-mediated RNAi knockdown of PrP by RNAi proved to be the first therapeutic application of RNAi against prion protein. In vitro studies have demonstrated that PrP^{Sc} replication was inhibited. Animals such as goats, cattle, and mice have been treated with RNAi expressed virally. A study by Pfeifer and colleagues demonstrated that anti-PrP^{C} short hairpin RNA (shRNA) is transfected into neuronal or embryonic stem cells, integrated into chromosomal DNA, and then transcribed by these cells. Upon release into the cytoplasm, Dicer processed anti-PrP^{C} shRNA into siRNA, which was then converted into siRNA. The activation of the RISC PrP mRNAs was degraded, which was in turn followed by a reduction in the expression of PrP^{C} and, thus, a decrease in the accumulation of PrP^{Sc} was noted. This resulted in a significant improvement in the survival time following prion infection. A novel avenue for treating prion disease may be opened by using RNAi as a potential therapeutic candidate [42]. The RNAi therapeutic approach offers a significant advantage over previous treatments for prion diseases, as it targets the mRNA of the prion, which has the same primary sequence across all known prion strains within a species. Therefore, this suggests RNAi could be effective against similar variants [43]. The RNAi strategy for silencing the PrP gene is depicted in Fig. 2. Hsp70 chaperones were identified as a key regulator of prion protein stability in a functional genomics screen using shRNA. This study suggests Hsp70 inhibition as a potential therapeutic approach for prion disease [44]. The study reported by Zheng et al. revealed that PHB2 promotes

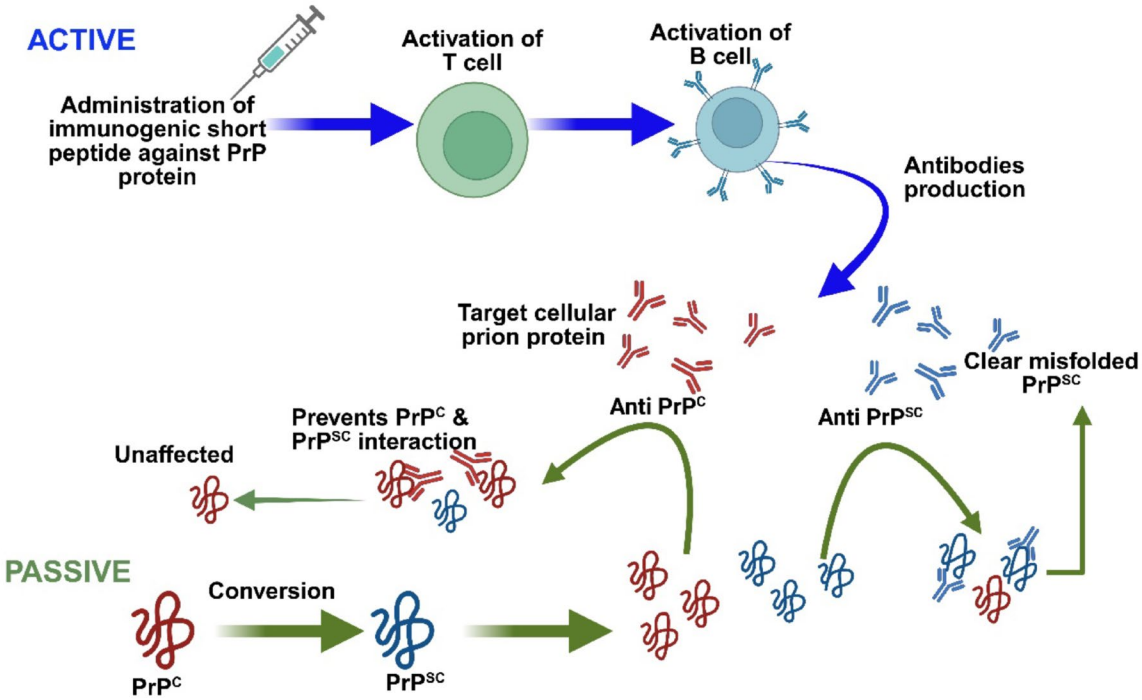


Fig. 1 Comparison of active and passive immunotherapy strategies against prion diseases. In active immunotherapy the activation of T cells, and further B cells produce antibodies against the cellular soluble protein PrP^{C} and prevents its conversion to the misfolded for PrP^{Sc}. In passive targeting the interaction between the cellular PrP^{C} and misfolded PrP^{Sc} is prevented and antibodies are raised against PrP^{Sc} to clear them from the circulation

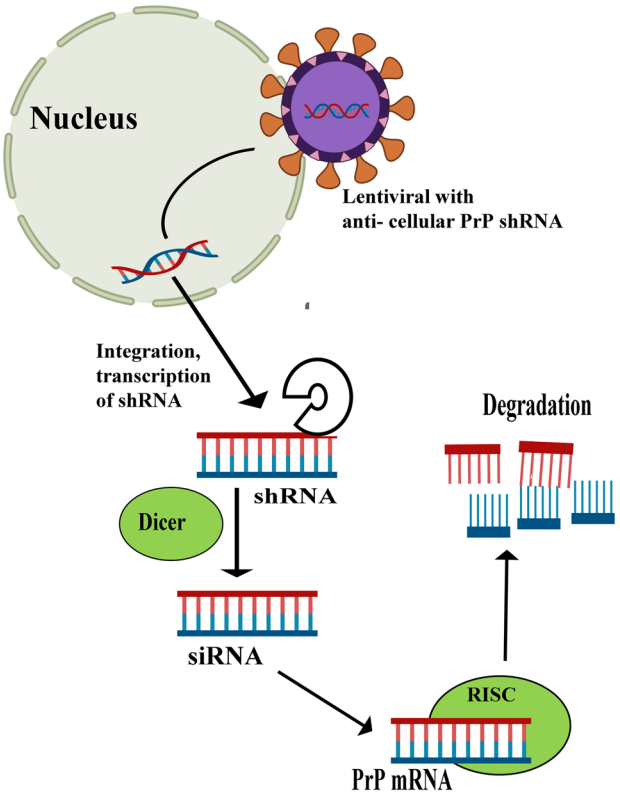


Fig. 2 RNAi strategy by using lentiviral shRNA. The degradation of PrP happens by the RISC complex. Upon release into the cytoplasm, Dicer processes anti-PrP^{C} shRNA into siRNA, which is then incorporated into the RISC complex. The activated RISC degrades PrP mRNAs, leading to a reduction in PrP^{C} expression and, consequently, a decrease in the accumulation of PrP^{Sc}

PINK1/Parkin-mediated mitophagy in neurons exposed to PrP106-126, reducing mitochondrial damage and neuronal death [45]. Another study demonstrated that *Prnp* and *Sprn* double knockout mouse embryos exhibited transcriptomic stability and decreased immune activation after exposure to shRNA lentiviral vectors [46].

Antisense oligonucleotides

Antisense oligonucleotides (ASOs) are one of the most promising gene silencing strategies being investigated for prion disease. ASOs are short, chemically altered nucleotide strands that attach to target genes of mRNA[47]. This leads to mRNA degradation, which lowers the amount of the encoded protein development. In the prion disease model, ASOs are specially developed to target PRNP (mRNA), which reduces the production of the prion protein and is also essential for the propagation of the pathogenic isoforms [48]. The study conducted by Friberg et al. has shown that intracerebroventricular infusion of ASO 771 lowered brain PrP^{C} mRNA and increased survival rate in RML prion-infected

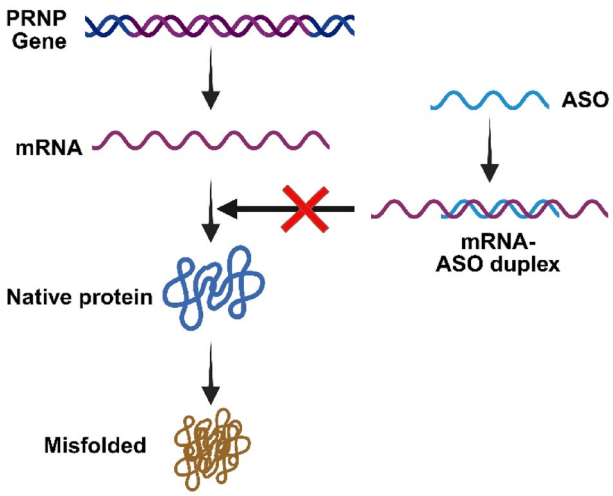


Fig. 3 Mechanism of ASO mediated gene silencing of prion protein expression. ASOs target the PRNP (mRNA), reducing the production of the PrP^{C}, and therefore, decreases the accumulation of PrP^{Sc}

mice [49]. PRNP gene silencing through intraventricular ASO administration showed significant results in prion-infected mice [50]. Another study demonstrated that PRNP gene targeting reduced prion protein levels and extended the lifespan in prion-infected mice [51]. A single intravenous dose of zinc finger repressors (ZFRs) suppressed PrP expression, reduced neuronal gene expression, and prolonged the survival of prion-diseased mice [52]. Prion infected mice that were treated with ASO showed significant improvements in survival rate up to 98%, supporting the development of ASO as a therapeutic approach before and after disease development [53]. The ASO based therapeutic mechanism depicted in Fig. 3.

Anti-aggregation compound

In about one in a million people, normal cellular protein is converted into misfolded prion aggregates that can destroy neurons. Although extensive research has been conducted, how normal cellular proteins convert into abnormal proteins remains unresolved, leading to toxicity when the cellular system fails to repair or remove these misfolded proteins [54, 55]. Such abnormal deposition is the hallmark of several neurological disorders, including prion and Creutzfeldt-Jakob disease. Therefore, it is necessary to screen for a compound that can inhibit protein aggregation in prion diseases [56]. In amyloidosis management, many natural enzymes within the serine protease group have demonstrated in vitro and in vivo amyloid degradation [57–62]. ZnO nanoflowers have also shown the degradation of insulin amyloids, which share similar structural homology with the amyloids responsible for AD and prion disease [63]. Several nanostructures have been reported to be effective in treating metal-induced

AD and Parkinson's disease [64]. Sulfated low molecular weight chitosan, isolated from marine sources, is neuroprotective in zebrafish models of PD [65] and in AD [66]. Over the past 30 years, scientists have examined several chemical and natural compounds for their possible anti-prion effects [67]. Among them, only a small number of anti-prions have undergone trials in patients with human prion diseases. Nano-based small molecule inhibitors have also been developed to reduce toxicity and promote the degradation of prion aggregates [56, 68]. The effects of some chemical and natural-based agents on prion disease management are discussed below.

Chemical-based anti-prion agents

Congo red (CR) is a traditional diazo dye used for histological studies and is highly specific for protein fibrils with a β-sheet conformation. These dyes are usually aromatic, heterocyclic compounds, a sodium salt of benzidinediazo-bis-1-naphtylamine-4-sulphonic acid (formula: C32H22N-6Na2O6S2). Congo red was discovered in 1883 by chemist Paul Bottiger, who tried to synthesize a substance that could be used as a pH indicator in 1885. This dye was later named Congo red [69, 70]. In 1886, Congo red was used as a pH indicator to detect acid content in animal intestinal tracts. Since then, Congo red has been used to identify amyloids, and it also possesses anti-prion properties that prevent the production of PrP^{Sc} [71]. Dimethyl sulphoxide (DMSO) is an organosulfur compound and an aprotic solvent that dissolves in both polar and nonpolar compounds [72]. Due to its amphiphilic nature, DMSO has both hydrophilic and lipophilic properties. DMSO was used as a chemical chaperone and a protein-stabilizing solvent that delayed the production of PrP^{Sc} in scrapie-infected mouse neuroblastoma cells [73]. Ethanolamine is a novel chemical compound with high anti-prion activities [74]. Moreover, it is naturally present in every cell, and the concentration of this compound varies in blood, breast milk, and the gastrointestinal tract. It is a glycosylphosphatidylinositol-anchored protein (GPI-AP) component essential for cell viability. Ethanolamine is also considered a growth-stimulating factor that stimulates the rapid growth of mammalian cells, and it also plays a significant role in the growth of hybridoma cells [75]. This newly developed anti-prion compound showed effective results in infected N2aC24L1-3 cells by reducing the PrP^{Sc} levels. Based on the dose-dependent model, oral administration of ethanolamine exhibited significantly longer times of survival in prion-infected mice [76]. Anle138b is a chemical agent that has been demonstrated to have anti-aggregating actions against numerous proteins linked to neurodegenerative diseases, such as tau, synuclein, and PrP [77]. It is another small molecule that inhibits PrP^{Sc}. It has recently been in the clinical trial for synucleinopathies and has already cleared the phase I clinical trial [78]. Wagner et al. (2013) reported that anle138b has been studied in vitro against sCJD and vCJD as well as in vivo against mouse-transmitted sheep scrapie [79]. Pentosan polysulfate (PPS) is a sizeable, linear polymer with an anionic charge and looks similar to the heparin structure. Several studies have shown that it inhibits the accumulation of PrP^{Sc} in prion-infected cells and extends survival in animal models. It has even been shown to improve patient survival rates. However, its clinical application is limited by poor blood–brain barrier (BBB) penetration, which remains a major drawback [80, 81]. PPS is synthesized chemically by sulfonating a xylan obtained from a beech tree called β-(1-4) xylan. This xylan backbone can be replaced with methyl glucopyranosyl uronic acid units that are glycosidically connected to the 2-position of the main chain, and it has fibrinolytic activity and anti-coagulant qualities [82]. Methylene blue (MB) dye belongs to the phenothiazine class and is a heterocyclic aromatic chemical compound. The Food and Drug Administration has approved this compound for oral or intravenous treatment of methemoglobinemia, ifosfamide-induced toxicity, malaria, and vasoplegic syndrome, as well as the visualization of neural tissue during surgery. This compound crosses the BBB, thereby effectively targeting the neuronal tissues. Additionally, the action of MB was shown to target the native structure and the aggregation of a model lysozyme, an amyloidogenic protein [83, 84].

Quinacrine (Qx) is an aminoacridine derivative developed in the 1920s, which is used chiefly as an anti-malarial and anthelmintic drug. Several viruses, including Ebola and Zika, have been proposed to be treated with this small molecule [85, 86]. It was also found that quinacrine significantly reduced the tissue damage caused by amebic hepatitis by 97% [87]. This drug has been proposed along with other chemical based drugs for possible Prion disease management [88]. Previous studies in 2003 have examined quinacrine's capacity to interact with PrP peptide aggregates and reduce their resistance to protease digestion, as well as its ability to inhibit the in vitro transformation of normal prion protein (PrP^{C}) into the disease-associated form (PrPres). The effectiveness of quinacrine was also compared to that of chlorpromazine—another tricyclic compound—using various in vitro systems and a mouse model of bovine spongiform encephalopathy (BSE). Quinacrine was found to effectively prevent the initial formation of fibrillar prion proteins and the buildup of PrPres in ScN2a cells. Nevertheless, it showed no impact on the protease resistance of already formed PrP fibrils or PrPres derived from brain tissue, and only produced a "curing" effect in ScGT1 cells after prolonged exposure. In live animal studies, quinacrine exhibited no noticeable therapeutic effect, a finding that aligns with both recent experimental results and early clinical observations in humans. Although the compound can penetrate the blood–brain barrier, its use as a standalone treatment

for Creutzfeldt-Jakob disease (CJD) remains highly uncertain [89]. A total of 107 individuals diagnosed with prion disease—including 45 with the sporadic form, two iatrogenic cases, 18 variant cases, and 42 inherited cases—were enrolled through the UK's national referral system to study the effect of quinacrine. Participants were given the option to receive quinacrine at a daily dose of 300 mg, decline treatment, or take part in a patient-preference, open-label trial that included randomization to either immediate or delayed quinacrine treatment. The primary outcomes assessed were mortality and serious adverse events that were potentially or likely linked to quinacrine. This trial is registered under ISRCTN 06722585. Although quinacrine was generally well tolerated at the specified dosage (300 mg daily), it did not show a meaningful impact on the progression of prion diseases in this observational study [90]. In another study, it was reported that if quinacrine was used continuously, it created drug resistance prion formation [91]. A double-blind, placebo-controlled treatment trial with stratified randomization, funded by the NIH and the National Institute on Aging, was carried out at the University of California, San Francisco between February 2005 and May 2009 (ClinicalTrials.gov identifier: NCT00183092). Participants were randomly assigned in equal numbers to receive either quinacrine (300 mg daily) or a placebo. Inpatient assessments were conducted at the study beginning and were rescheduled at months 2, 6, and 12. At the two-month mark, those who returned for follow-up were given the option to switch to open-label quinacrine. The primary endpoint was survival from the time of randomization to the two-month follow-up. This interventional study offers Class I evidence that oral quinacrine at a dose of 300 mg per day does not enhance two-month survival in patients with sporadic Creutzfeldt-Jakob disease (sCJD) when compared to placebo. Notably, the trial also demonstrates that conducting rigorous, double-blind, placebo-controlled randomized studies in prion disease is feasible [92].

Flupirtine is a non-opiate analgesic drug belonging to the triaminopyrimidines class. It is a potent drug that also has neuroprotective, sedative, and antiepileptic actions, which are important pathological and clinical traits of NCLs. Treatments with flupirtine prevented apoptosis in the neurons of chronically stressed rodents [93]. Doxycycline is an anti-prion agent utilized in amyloid aggregation [34]. Table 4 summarizes the different chemicals that can offer promising strategies as anti-aggregation compounds for managing prion disease.

Natural compound-based anti-prion agents

Several natural compounds have been proposed to have anti-amyloid activity [105] including lumbrokinase from earthworms [58, 59, 61, 106] and serine proteases [60, 62]. Curcumin is made up of yellow pigment obtained from the rhizome of turmeric, a plant belonging to the ginger family. This pleiotropic molecule prevents the accumulation of misfolded proteins by directly binding to them in many neurodegenerative diseases. It also contributes towards homeostasis maintenance of the inflammatory system, speeds up the removal of toxic aggregates from the brain, scavenges free radicals, chelates iron, and triggers the production of antioxidant response elements. Recently, many researchers have shown enhanced interest in using curcumin to either stop or delay the onset of neurodegenerative illnesses [107]. Resveratrol is a natural polyphenolic phytoalexin that occurs in numerous fruits and vegetables like grapes, berries, peanuts, etc. Resveratrol exhibits anti-allergic, anti-aging, antioxidant, and neuroprotective activities. It also prevents prion infection and replication in in vivo and in vitro models [108, 109]. Tauroursodeoxycholic acid (TUDCA) is a hydrophilic bile acid, mostly created when taurine is conjugated with ursodeoxycholic acid. TUDCA is capable of penetrating the BBB, and the US FDA has approved TUDCA for treating liver conditions such as cirrhosis and cholestasis. Through lowering the LPS-induced apoptosis and deficits in synaptic plasticity, TUDCA therapy alleviated cognitive impairment and neurotoxicity in mice. TUDCA has also been demonstrated to activate nuclear factor erythroid 2-related factor 2 (Nrf2) signaling, which can increase mitochondrial biogenesis and early neurogenesis while reducing damage caused by reactive oxygen species (ROS) [110].

Melatonin is a neuroendocrine hormone secreted by the pineal gland in mammals, including humans. Melatonin is essential for controlling circadian rhythms and performs a variety of other tasks. In numerous experimental models, including AD, melatonin has been established to suppress microglial activation and decrease proinflammatory cytokine levels [3]. Polydatin, also known as piceid (3,4,5-trihydroxystilbene-3-β-D-glucoside), is a monocrystalline stilbene derivative that is obtained from the roots of *Polygonum cuspidatum* and is recognized as a natural precursor of resveratrol. It is known to have anti-inflammatory, immunoregulatory, anti-oxidative, and anticancer effects and neuroprotection activity. It has shown promising anti-amyloid activity against human prion peptides [24]. Spermidine is a natural active polyamine that is created from putrescine or a breakdown of spermine. It exists in mammalian cells, where aging causes a reduction in intracellular levels. Generally, nutritional supplementation of this agent elevates blood polyamine levels in mice and humans. Based on an autophagy-dependent manner, spermidine extended lifespan in both in vivo and in vitro studies and has demonstrated anti-amyloid activity [111, 112]. The active molecules present in the deep-sea vent microorganisms were isolated by Bitop AG, Germany, which consisted of ectoine, hydroxyectoine, mannosylglyceride, and mannosylglyceramide

Table 4 Chemical-based anti-prion compounds and their effect on prion disease

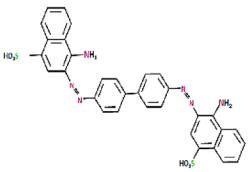
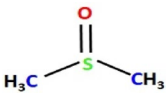
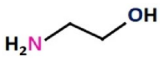
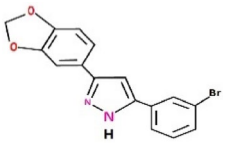
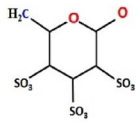
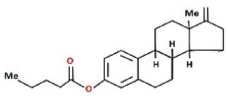
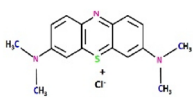
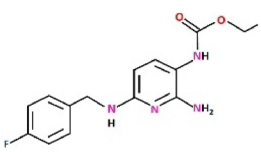
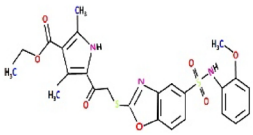
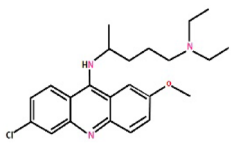
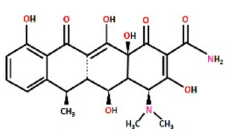
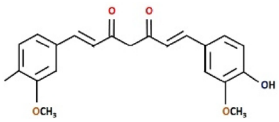
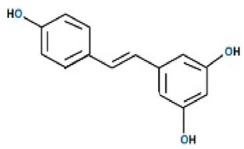
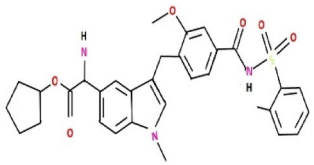
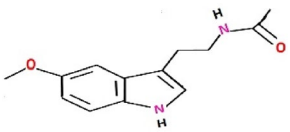
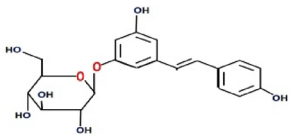
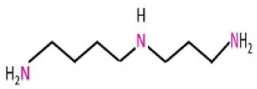
Structure	Compound	Class	Target	Levels	Preclinical/ clinical trials	Reference
	Congo red	Diazo dye	PrP^{C}/ PrP^{Sc}	in vitro, in vivo	Preclinical	[94]
	Dimethyl Sulphoxide	Aprotic solvent	PrP^{C}	in vitro, in vivo	Preclinical	[72, 95]
	Ethanolamine	Small organic molecule	PrP^{C}	in vivo	Preclinical	[76]
	Anle138b	Diphenylpyrazole derivatives	PrP^{C}	in vitro, in vivo	Preclinical	[77, 78]
				in human	Clinical	[96]
	Dextran sulphate	Sulphated polyanions	PrP^{C}	in vitro, in vivo	Preclinical	[97]
	Pentosan polysulfate	Sulphated polyanions	PrP^{C}	in vitro	Preclinical	[80, 98]
	Methylene blue	Phenothiazine derivative	PrP^{C}	in vitro	Preclinical	[84]
	Flupirtine	triaminopyrimidines	PrP^{C}	in vivo	Preclinical	[99, 100]
	BMD42-2910	Benzoxazole derivative	PrP^{C}	in vivo	Preclinical	[101]
	Quinacrine	Acridine derivative	PrP^{C}/ PrP^{Sc}	in vitro, in vivo	Preclinical	[102]
				in human	Clinical	[41, 92]
	Doxycycline	Tetracycline	PrP^{C}	in vitro, in vivo	Preclinical	[103]
			PrP^{C}	in human	Clinical	[104]

Table 5 Natural-based anti-prion compounds and their effect on prion disease

Structure	Compound	Class	Target	Level of study	Preclinical/ clinical trials	Reference
	Curcumin	Curcuminoid	PrP^{C}	in vitro, in vivo	Preclinical	[114–116]
	Resveratrol	Stilbenoid	Autophagy	in vitro in vivo	Preclinical	[117] [118]
	Tauroursode-oxycholic acid	Bile acid	PrP^{C}	in vitro, in vivo	Preclinical	[119]
	Melatonin	Neuro-endocrine hormone	Autophagy	in vitro, in vivo	Preclinical	[120] [121]
	Polydatin	Resveratrol glycoside	PrP^{C}	in vitro	Preclinical	[24]
	Spermidine	Polyamine	PrP^{Sc}	in vitro	Preclinical	[122]

(MGA). Among these molecules, ectoine and MGA could effectively degrade the prion peptide PrP 106–126 in vitro [113]. Table 5 summarizes the natural compounds that show effectiveness in controlling prion peptide degradation.

β-sheet beaker

In the past few years, β-sheet breakers (BSB) have emerged as the prototypical family of drugs that prevent and reverse protein misfolding and aggregation. When peptide interactions occur, Aβ amyloidogenic intermediates undergo hydrophobic interactions, resulting in a β-sheet conformation [123]. The BSB peptides are an attractive family of peptide-based inhibitors, as they specifically target the β-sheet structure of Aβ peptide, which is linked to neurotoxicity in AD [124]. In 1996, Soto developed 11 residue peptide inhibitors (iAβ11 and RDLPFFPVRID) based on the Aβ17-21 sequence [125]. In 1998, a five residue β-sheet breaker was synthesized explicitly by modifying the A21 and V18 of the fragment. iAβ5 (LPFFD) effectively inhibited the Aβ aggregation and neuronal death, and this peptide showed potential action in rat brain models [126]. In 2000, Soto synthesized β-sheet breaker peptide (iPrP13) that reversed the PrP^{Sc} [127]. These peptides are mainly used to degrade preformed amyloid fibrils and inhibit the amyloid Aβ conversion. A β-sheet breaker peptide (iAβ5: LPFFD), which had only five residues, was tested in human neuroblastoma cells. The results showed that the peptide was capable of resisting neuronal cell death that was induced by the β-sheet-rich oligomeric Aβ structures. A step forward, the β-sheet breaker peptide activity in vivo was assessed using two animal models. In the first model, the induction of amyloid deposits was executed by injection of non-aggregated Aβ1-42 directly into the rat brain. The second experiment was conducted using the same rat model, in which iAβ5 was used to reduce the preformed Aβ fibrils. The results showed a significant size reduction in the preformed Aβ fibrils post injection of the iAβ5 into the cerebral amygdala. The iAβ5 was injected 8 days after the injection of Aβ at the same place, resulting in a reversion of the various associated cerebral histopathological changes, such as neuronal shrinkage and microglial

activation, etc. On the other hand, there was no significant effect analyzed after injection of unrelated peptides (used as controls) to the animals under the identical conditions [128]. Thioflavin T (ThT) is a dye that specifically binds to β-sheet rich proteins and emits fluorescence. ThT binding assay is a widely used fluorometric technique to measure efficacy in vitro, and was utilized to quantitatively establish the activity of numerous β-sheet breaker peptides, which were further qualitatively demonstrated by electron microscopic examination [57]. Sinopoli et al. developed the LPYFD pentapeptide, which reduced τ aggregation, nerve cell decay, and Aβ42 induced cell mortality. The rational modification with appropriate moieties is a promising strategy to improve BSB activity against Aβ42 aggregates [129]. Khairnar et al. 2023 demonstrated that the modified cyclic β sheet peptide showed excellent anti-amyloidogenic activity against Aβ1–42 fibril formation [130]. The synthetic peptide inhibited the Aβ1-40 aggregation and disrupted the aggregates in a dose-dependent manner. Therefore, these results suggest that the breaker strategy can be used as an excellent therapeutic against AD [131]. Similar encouraging effects on AD are shown with the KVLFF peptides amalgamated with nanoparticles. The result revealed that the nanoparticle combined peptide was more potent in reversing Aβ aggregation [132]. The β-sheet beaker strategy for blocking conformational changes in PrP is depicted in Fig. 4.

Stem cell-based therapies

Stem cell grafting therapies treat neurodegenerative diseases like lateral sclerosis and Huntington's. Mesenchymal stem cells, fetal neural cells, adult neural cells, and embryonic stem cells are some of the stem cells that are used to treat prion disease [133]. Recently, numerous studies on mesenchymal stem cells have shown effective results in treating strokes, brain tumors, and neurodegenerative diseases, including amyotrophic lateral sclerosis, Alzheimer's, and Parkinson's in animal models. Mesenchymal stem cells (MSCs) are fibroblast-like cells distinguished by their ability for differentiation and self-renewal in mesodermal tissues. These cells can also undergo in vitro trans-differentiation to become undifferentiated cells expressing PrP^C and neuron-like cells [134]. Song et al. (2009) reported that human bone marrow-derived MSCs (BM-MSCs) were transplanted intracerebrally or intravenously, which prolonged the survival rate of prion-infected mice. These transplanted MSCs migrated to lesions in the brain and produced neurotrophic factors like Brain-derived neurotrophic factor (BDNF) and neurotrophins (NT) 3 and 4/5. These findings reveal that

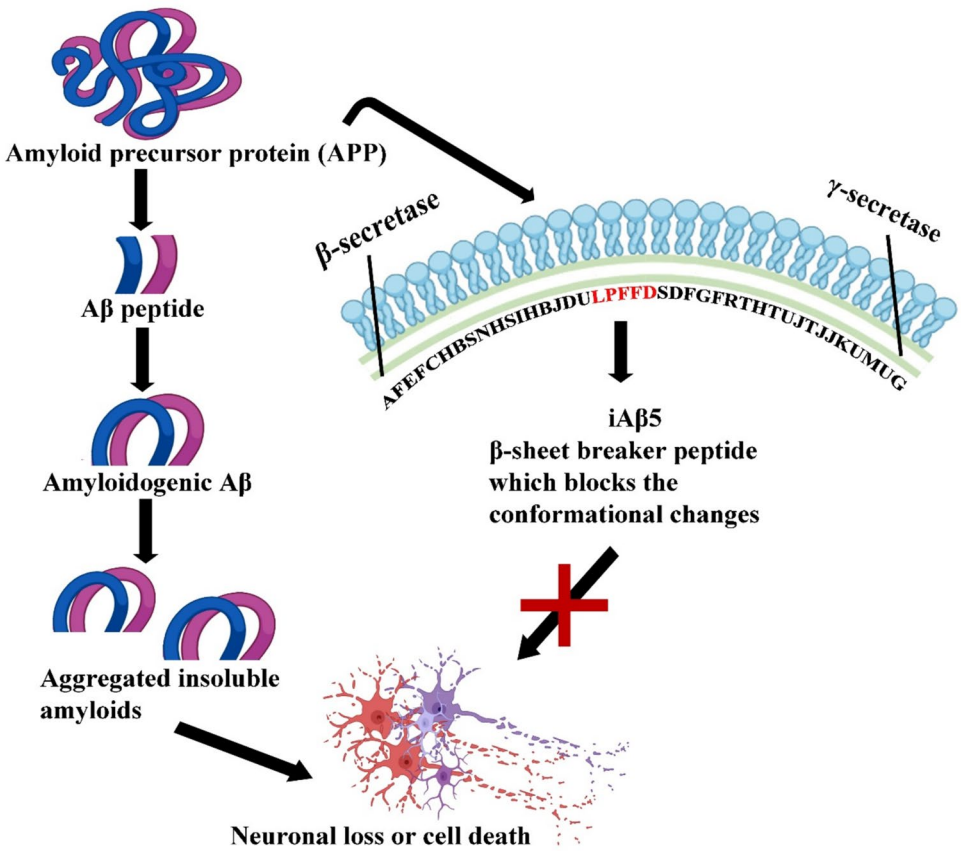


Fig. 4 β-sheet breaker against prion/ amyloidogenic Aβ aggregation. The conformational changes of amyloid Aβ are blocked by the β-sheet breaker peptide, thereby protecting the neuronal loss

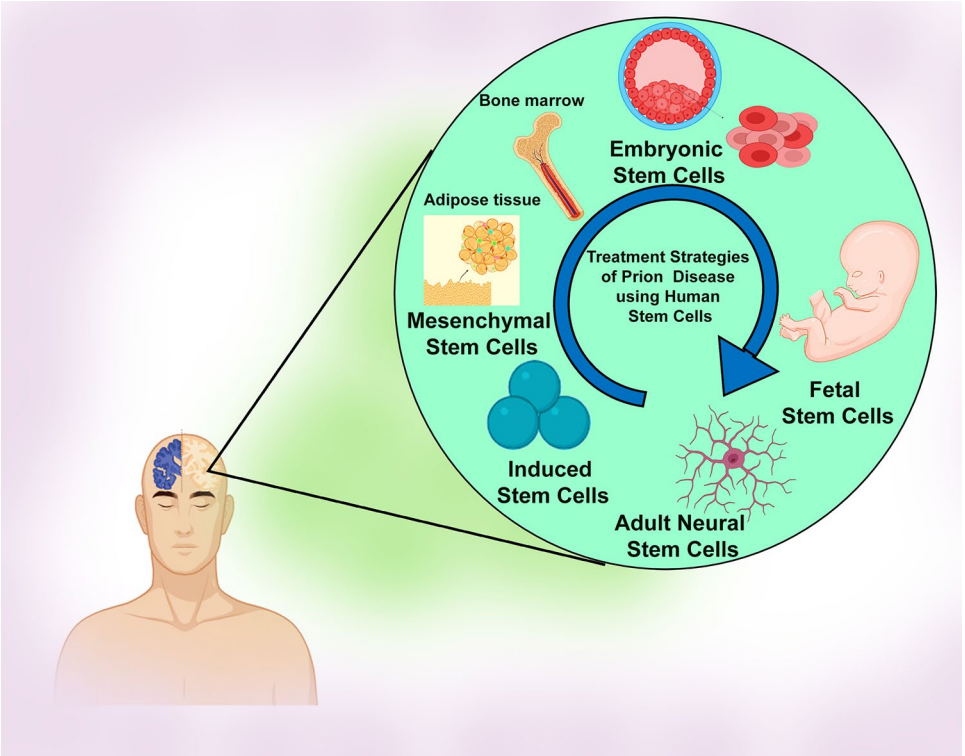


Fig. 5 Stem cell therapies in prion disease. Different types of stem cells, like induced pluripotent stem cells, mesenchymal stem cells, adult neural stem cells, fetal stem cells, and embryonic stem cells for transplantation in the management of amyloidosis

bone marrow-MSCs from humans can protect against prion disease [135]. Recent research indicated that the recombinant form of PrP^C and its cleavage products are involved in the neural differentiation and neurogenesis processes [136]. In another study, MSCs were intravenously administered in both young and aged 3xTg-AD animal models of AD, resulting in decreased tau phosphorylation at S214, T205, T231, and neuroinflammation. The number and timing of MSC injections showed a neuroprotective impact on the 3xTg-AD mouse model of AD [137]. MSCs have demonstrated promising results in preclinical studies of AD. MSCs were experimented with to treat AD, where nine patients took part in a phase I assessment of MSC injection directly into the human brain. This experiment validated the viability and safety of MSC injection into the human brain [138]. Neural stem cells (NSC) from various sources can produce new neurons and glia, and they also replace lost cells. These cells were capable of secreting trophic factors such as BDNF and glial cell-derived neurotrophic factors to promote endogenous healing [139] [140]. Generally, this type of neurogenesis is noted in two mammalian regions of the brain, such as the subventricular zone (SVZ) and dentate gyrus (DG), which are highly sensitive. Intranasal transplantation of human neuronal stem cells (hNSCs) exhibited increased neuronal differentiation and reduced amyloid accumulation by upregulating amyloid degrading enzymes. Further, neprilysin expression decreased neuroinflammation, pericytic and synaptic loss, and restored cognitive function in an APP/PS1 transgenic AD mouse model. The greatest potential existed in the use of human NSCs for intranasal transplantation and was considered a non-invasive therapy option for AD that lowered amyloid levels in animal models of AD by blocking the activities of cathepsin B, plasmin, and insulin-degrading enzyme [141]. Most of the treatment strategies were found for AD which could be extrapolated for prion diseases in the future.

Embryonic stem cells (ESCs) are pluripotent stem cells (PSCs) that are capable of self-renewal and differentiation into different kinds of cells. Both embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) are types of pluripotent stem cells (PSCs). It is widely acknowledged that cell-based therapeutic products (CTPs), including PSC-derived products, are innovative pharmaceuticals as opposed to small-molecule drugs and antibody drugs [142]. A significant technical breakthrough in cell replacement-based therapy has set apart several studies. Transgenic mice (TgCJD mice) were treated with NPC-centered treatment that replicated the human E200K PrP gene mutation and caused a specific form of hereditary CJD. The neural progenitor cells (NPC) were produced from the brains of TgCJD or mouse embryos, and the tNPC grafting was performed on newborn TgCJD mice. In both types of NPC animals, compared to non-transplanted mice, a significant delay in disease progression was seen during a 10-month follow-up. The disease incubation period could be extended by 35% by either form of the NPC. In

the brains of the animals with the grafts, there was also an increase in the endogenous NSCs. According to this, the transplanted cells appeared to have a pro-neurogenic impact, and the endogenous NSCs of TgCJD animals did not accumulate PrP^{Sc}. The use of TgCJD mice's NPCs as a transplant for the mice also resulted in no prions being transmitted [143]. Figure 5 depicts cell-based therapy as a possible treatment strategy for prion disease.

Conclusion

Prion diseases are a group of neurogenerative diseases caused by aggregation, protein misfolding, tissue accumulation, and induced conversion of PrP^{C} to PrP^{Sc} forms. Using modern scientific advancements, researchers have developed vast numbers of therapeutics that can prevent protein misfolding. Recently, a substantial amount of literature has been published as a result of various research methodologies. These include cell therapy, pharmacotherapy, immunotherapy, and some chemical and natural-based anti-prion agents, which were also tested in animal studies, some in humans, and some in clinical trials. Even though there is no effective treatment for prion illness, only drugs that reduce the symptoms of the condition are being applied. This review covers prophylactic and therapeutic approaches for prion diseases and recent therapeutic research and development. Furthermore, in the future, we can expect new anti-prion medicines to be discovered with less toxicity and higher bioavailability based on the results of existing therapies, which may be effective in treating prion disease.

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Author contributions SU, AG, KG: conception and design, as well as the drafting of the paper. SU, AG, KG: revising it critically for intellectual content and the final approval of the version to be published. All authors agree to be accountable for all aspects of the work.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interest The authors declare no competing interests.

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