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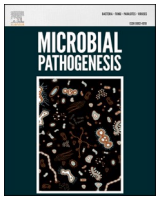

The infectious potential of protein misfolding: insights from cross-over studies of prion diseases and common neurodegenerative disorders

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ABSTRACT

In recent years, important progress has been made in the study of the pathogenesis of neurodegenerative diseases, especially the role of protein misfolding and aberrant aggregation in the development of diseases has attracted much attention. As a class of zoonotic infectious neurodegenerative diseases caused by prion protein misfolding and aggregation, prion diseases, with their unique transmission characteristics, have provided important insights for the study of other neurodegenerative diseases. A growing body of research has shown that similar abnormal protein aggregation phenomena occur in common neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD). These misfolded proteins exhibit striking similarities to prions in terms of seeding capacity, cytotoxicity, and propagation properties. Further investigation into the prion-like behavior of these aberrant proteins in neurodegenerative diseases can offer new directions for diagnosis and treatment. Recent studies have demonstrated that AD can be transmitted through medical routes, which warns us that neurodegenerative diseases are potentially infectious and deserve further attention and research. This article systematically reviews the pathological features and transmission mechanisms of abnormal proteins in prion diseases and other neurodegenerative disorders, aiming to provide a new perspective for the prevention and treatment of these diseases. Moreover, this research holds significant implications for public health and clinical practice. By revealing the potential transmissibility of neurodegenerative diseases, it can help improve medical protocols and reduce the risk of iatrogenic transmission.

1. Introduction

Prion diseases, also known as transmissible spongiform encephalopathies (TSEs), are caused by prions and are characterized by hallmark features such as spongiform encephalopathy, neuronal damage or loss, glial cell proliferation, and the accumulation of prion protein aggregates of varying sizes [1]. In recent years, the researches into the molecular mechanisms of neurodegenerative diseases have revealed that diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), chronic traumatic encephalopathy (CTE), and amyotrophic lateral sclerosis (ALS), despite exhibiting different clinical symptoms, is thought to be the result of misfolding and aggregation of abnormal proteins, leading to cellular dysfunction, loss of synaptic connectivity, and brain damage [2]. More strikingly, these abnormally aggregated proteins can be used as templates for their own replication by monomer addition, exhibiting seeding ability and cytotoxicity similar to prions. Notably, prion propagation breaks the traditional framework of pathogen perception - no nucleic acid involvement is required, and cross-species infection is achieved only through protein conformational changes and thus aggregation. Nowadays, some *in vivo* and *in vitro* experimental evidences also suggest that pathological proteins of neurodegenerative diseases are capable of spreading from cell to cell, which have prompted academics to link the prion mechanism to these pathological proteins, and to re-examine the fundamental question of whether neurodegenerative diseases are potentially infectious. This scientific controversy has recently led to a breakthrough, Banerjee et al. [3] confirmed through their study on the treatment of patients with cadaveric human growth hormone (c-hGH) that AD, like Creutzfeldt Jakob disease (CJD), can be transmitted through iatrogenic forms. This also warns us that AD is a potential infectious disease. The discovery of neurodegenerative diseases, a major health issue for the world's aging population, not only challenges the traditional perception of neurodegenerative diseases as 'non-contagious', but also forces public health systems to establish new risk assessments and impose stricter requirements for the control of

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surgical devices. The aim of this study is to analyse the pathological characteristics and transmission patterns of prion diseases, to elucidate their pathogenic mechanisms and transmission routes, and then investigate the prion-like behaviour of heterologous proteins in neurodegenerative diseases to reveal their potential infectiousness, so as to provide scientific evidence and early warning for the development of major public health prevention and control strategies. At the same time, this study will help to better understand the mechanism of the occurrence and development of neurodegenerative diseases, and provide new perspectives for the prevention and treatment of the diseases.

2. Methods

Literature selection criteria: In this study, we systematically investigated the pathological characteristics and transmission mechanisms of abnormal proteins in prion diseases and other neurodegenerative disorders using literature research. We searched the literature on prion diseases and neurodegenerative diseases in PubMed and Web of Science, and prioritized papers with high citation rates to ensure academic authority, and expanded the scope of the literature through 'related papers' and 'cited papers' to ensure comprehensive coverage of the literature in the research field.

Literature search process: In this study, we investigated neurodegenerative diseases based on the relevant properties of prion diseases. Firstly, we searched using the terms 'prion disease', 'prion' in PubMed and Web of Science, then 'protein aggregation mechanism', 'prion propagation', and specific prion diseases (e.g., "prion disease of sheep, mad cow disease, chronic wasting disease, Crohn's disease, Creutzfeldt-Jakob disease", etc.) in PubMed and Web of Science. A search was conducted to identify and download literature related to the study topic based on the title and abstract. For neurodegenerative diseases, the terms 'neurodegenerative diseases', 'Alzheimer's disease', 'Parkinson's disease', and 'amyotrophic lateral sclerosis' were searched in PubMed and Web of Science to filter literature related to protein misfolding and aggregation, and infectiousness by the title and the abstract, and were download. In addition, the search was refined to relevant disease-specific abnormal proteins (e.g., 'Aβ, Tau, A-syn, TDP-43'), and the references related to the protein aggregation mechanism and propagation properties were screened according to the abstracts. Then, we read the references and conducted a round of screening, kept the references that were closely related to the research topic for classification, and added the cited literature in a timely manner. After the first round of reading, the framework of this study was determined with the existing research, and the idea of writing. Finally, the sections of literature were intensively read, further analysed, generalised, summarized the links, and the paper was written.

Year range: The literature spans 1957–2024, with a focus on recent studies from 2010 onwards to ensure that the review is cutting-edge.

Graphical treatment: Based on the literature analysis, added graphs and charts to support the illustration with the focus of the study. This study involves the association between prion diseases and neurodegenerative diseases, the transmission of diseases, etc. Therefore, integrating the relevant information and designing compositions to link up the parts so that readers can read and understand better. At the same time, the use of drawings to present the aggregation mechanism of misfolded proteins could be more clear and concise, and also reduced the redundancy of text. We used the Adobe Illustrator software (2023 version, Adobe Systems Incorporated, San Jose, California, USA). Tables were generated using the Word (2023 version, Microsoft Corporation, Redmond, Washington, USA). All figures and tables were developed based on the research findings from the literature.

3. Types, pathological characteristics, and infectivity of prion diseases

Prion disease is a fatal neurodegenerative disease caused by the misfolding and aggregation of normal prion protein (PrPC) into PrPSc, which is zoonotic and has unique infectivity. These infectious proteins have led to widespread epidemics, including scrapie, bovine spongiform encephalopathy (BSE), Kuru, Creutzfeldt-Jakob disease (CJD), *Gerstmann*-Straussler syndrome (GSS), fatal familial insomnia (FFI) and others. Their clinical manifestations mainly include behavioral abnormalities, motor dysfunction, cognitive impairment, and ataxia. Due to the different symptoms and pathological changes exhibited by different species infected with prions, it is usually necessary to classify them according to the infected species and disease characteristics.

3.1. Scrapie

Scrapie is the earliest recorded prion disease, mainly infecting sheep and goats, and is the original model disease for studying the pathogenesis and neuropathological changes of TSE. Prions can cause degenerative changes in the central nervous system (CNS) of sheep and goats, depending on the type of itch disease and the prion protein gene (PRNP) of the host. However, the main lesions include the vacuolization of neuronal nuclear and gray matter membrane, neuronal degeneration, gliosis (mainly astrocytes), and amyloidosis. The main brain regions affected are the diencephalon, midbrain, pons, medulla oblongata, and cerebellar cortex. There are two main forms of scrapie, classical scrapie and nonclassical scrapie. The distribution of brain damage is different between the two [4,5]. In sheep and goats, infectivity is widely spread within the body, not only in the nervous system, but also in lymphoid tissue, spleen, intestinal wall, and other tissues that contain infectious factors. In the 1930s, researchers first observed and recorded experimental transmission of scrapie in sheep after long-term inoculation with infectious substances [6]. Since then, studies have confirmed interspecies transmission of itch, such as vertical transmission, the lambs are exposed to PrPsc by contact with the placenta and amniotic fluid of infected ewes and objects contaminated with these substances or by consumption of breast milk; ingestion of PrPsc from contaminated environments can lead to horizontal transmission of scrapie in sheep [7]. In addition, infected sheep also release PrPsc into the environment through saliva, urine, and feces. Gibbs et al. [8] demonstrated that the PrPsc pathogen can be transmitted to *Macaca fascicularis* by oral ingestion of infected brain, kidney, and spleen tissues. Naturally occurring scrapie was first detected in the gastrointestinal tract and lymphatic tissue of clinically normal animals, and this evidence also suggested that scrapie can be transmitted orally. Adams et al. [9] proposed the existence of semen and placental transmission mechanisms in sheep and goats through epidemiological, clinical, and experimental studies. Non-classical scrapie was first described in sheep in Norway in 1998 [4], and it typically occurred in older single animals [10]. Intracranial injection or oral administration of brain homogenate containing non-classical scrapie has successfully transmitted non-classical scrapie to sheep [11]. Non-classical scrapie is not easily transmitted in natural environments and there are no clustered cases. In addition to intra- and interspecific transmission, scrapie can also be transmitted across species among some small ruminants. It has been proven that the brain or oral and nasal inoculation of scrapie prions can cause diseases in North American *Odocoileus virginianus*, *Elaphurus davidianus*, *Procyon lotor*, etc. (Fig. 1), and the PrPsc immune phenotype recovered from *Elaphurus davidianus* vaccination is similar to that of scrapie, but different from isolates obtained from Cervidae with chronic wasting disease (CWD), indicating that scrapie is unlikely to be the source of CWD in *Elaphurus davidianus* [12]. However, the spread of scrapie has species barriers, such as dogs and pigs having a certain resistance to infection with scrapie. Experimental studies have shown that cattle also have a strong species barrier against scrapie pathogens. Oral administration of PrPsc isolated from diseased sheep did not cause disease, while brain inoculation with scrapie pathogens could cause disease, but the phenotype was different from that of BSE [13]. For the zoonotic nature of scrapie, studies have shown that the likelihood of humans suffering from scrapie

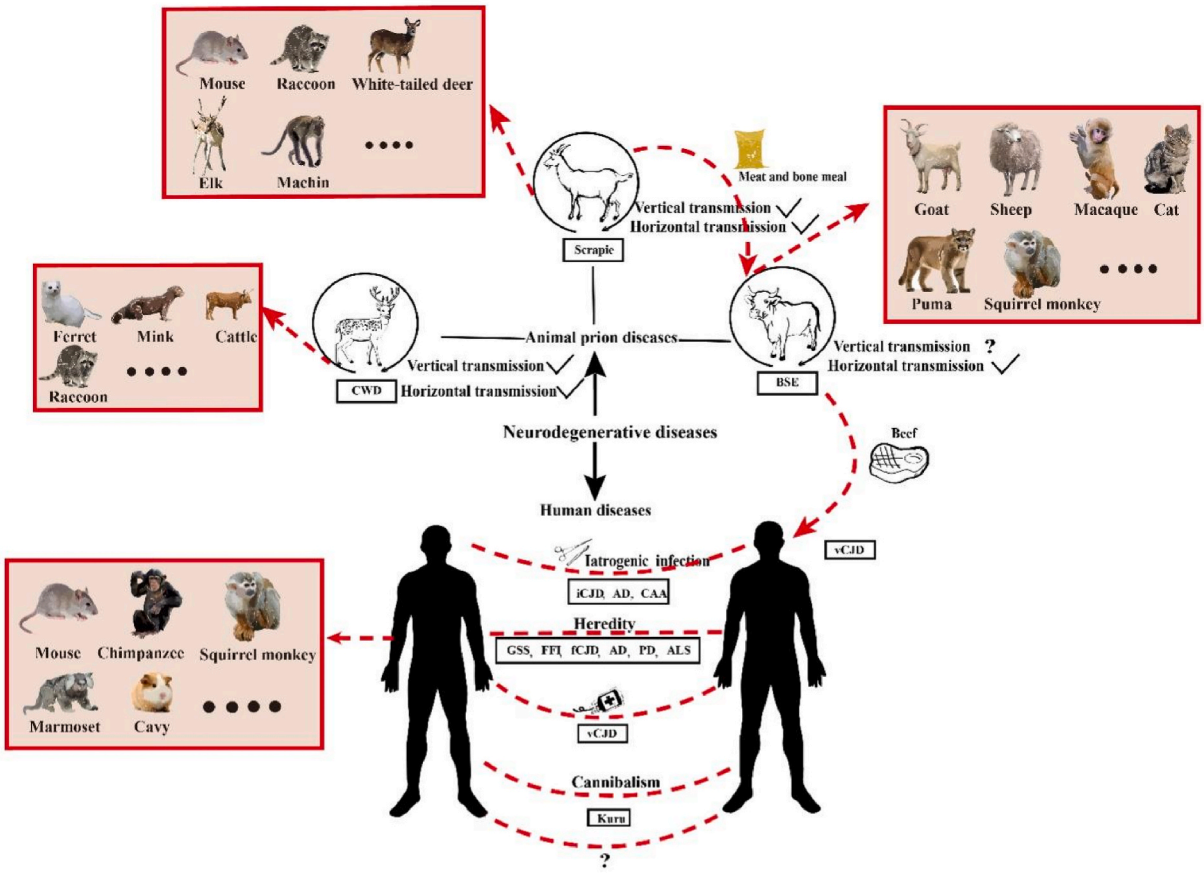

Fig. 1. The infectivity of neurodegenerative diseases. The upper part of the figure shows animal prion diseases and their infected species, the name of the disease is in the black box, the circle with arrow on the animal indicates that the disease can spread within the species, with the mode of transmission labelled next to it, and the box pointed by the red dotted arrow indicates the animal that the disease can spread across species. The lower part of the figure shows human prion diseases and common neurodegenerative diseases. The red dotted line between people indicates different diseases and their transmission routes, and the red box indicates the animals that can be infected. In this case more the species that the human prion disease can infect. The "?" at the bottom of the graph indicates uncertain human-to-human transmission modes.
CWD: chronic wasting disease; BSE: bovine spongiform encephalopathy; GSS: gerstmann straussler scheinker; FFI: fatal familial insomnia; CAA: cerebral amyloid angiopathy; iCJD: iatrogenic creutzfeldt-jakob disease; fCJD: familial creutzfeldt-jakob disease; vCJD: variant creutzfeldt-jakob disease; AD: alzheimer's disease; PD: parkinson's disease; ALS: amyotrophic lateral sclerosis.

was very low. The phenotype of prions isolated from human TSE patients was incompatible with those isolated from scrapie in sheep. However, research using transgenic mice overexpressing human PrPc has shown that these mice were affected by certain classical scrapie bacteria strains [14], indicating the potential for the zoonotic development of scrapie. However, the species barrier is large and the infection rate is extremely low. Currently, there is no evidence of scrapie spreading to humans.

3.2. *Bovine spongiform encephalopathy*

BSE, also known as mad cow disease, was first discovered in the UK in 1985. It was named BSE because the brain tissue of infected cows appeared spongy under an optical microscope [15]. This disease can cause spongy lesions in the bovine brain, clinically manifested as mental disorders, motor disorders, ataxia, muscle spasms, etc. Its infection is thought to have been transmitted to cattle through meat and bone meal, an industrial dietary supplement made from sheep, cattle, pigs, and chickens. High temperature disinfection can kill the traditional pathogens, but PrPSc can survive and infect cattle. After the report of BSE, it spread worldwide, causing huge losses to the cattle industry, and further expanding to cattle, felines, and primates in British zoos [16]. It was not until the UK banned animal feed made from ruminants in 1988, and Northern Ireland in 1989, that the number of cases significantly decreased [17]. Researchers have also suspected the vertical transmission of BSE. Although Castilla et al. [18] have achieved the vertical transmission of BSE in transgenic mouse models, there is no clear evidence that it can spread vertically in cattle. Hedman et al. [19] successfully demonstrated the experimental transmission of BSE in pigs through three administration methods: intracerebral, intraperitoneal, and intravenous injection. The disease has been transmitted to sheep and goats in experiments through intracranial inoculation with BSE preparations, or ingestion of bovine products infected with BSE prions. The transmission of BSE also has species barriers. For example, during the BSE crisis in the UK, many animals (cats, cougars, cheetahs) were infected with spongiform encephalopathy (Fig. 1), but no cases of the disease were observed in dogs [20,21]. This barrier was found to correlate with the degree of sequence homology between host PrP and inoculated PrP (sc), with only 7 differences in PrP between sheep and cattle, making sheep susceptible to BSE. BSE is the only proven zoonotic animal prion disease, and the prion that causes BSE can trigger variant Creutzfeldt Jakob disease (vCJD) in humans. In the early days, with the emergence of BSE, vCJD appeared in some parts of the UK and Europe, and some scientists suspected that BSE could spread to humans. Since then, a large number of studies have also confirmed this view. In March 1996, the CJD surveillance unit established in Edinburgh reported 10 cases of a new variant of CJD. 10 patients showed specific neuropathological features - spongy changes and PrP (sc) plaques, and the patients

were young, different from the previously described CJD disease, which increased the likelihood that these cases were linked to BSE [22]. Since then, numerous *in vivo* and *in vitro* cross-species experimental studies and epidemiologic evidence have supported the idea that vCJD is transmitted from BSE to humans. An observation of the brain lesion characteristics of a vCJD patient from France and two patients from the UK, as well as non-primates infected with BSE, showed that the lesion characteristics in the brains of the three individuals were identical, providing evidence that BSE pathogen strains have spread to humans in both the UK and France [23]. In a transmission experiment in which researchers intracerebrally injected BSE-infected bovine brain homogenates into crab-eating monkeys, all three infected animals developed clinical features similar to those seen in patients with vCJD, with the brains displaying similar neuropathology and PrPsc deposition [24]. Experiments have demonstrated that BSE can be transmitted to nonhuman primates such as *Macaca mulatta*, *Callithrix jacchus*, *Lemuridae*, and *Saimiri sciureus* (Fig. 1), either orally or by intravenous injection. All of these indicate that BSE and vCJD have indistinguishable transmission characteristics, and the pathogens of these two prion diseases are the same strain [25]. Recently, Konold et al. [26] inoculated brain homogenates from sheep with atypical scrapie into calves, demonstrating for the first time that TSE factors with BSE-like characteristics can be amplified in cattle inoculated with atypical scrapie brain homogenates.

3.3. Chronic wasting disease

CWD is believed to be highly transmitted in deer species, including *Odocoileus hemionus*, *Odocoileus virginianus*, *Elaphurus davidianus*, and *Alces alces* [27]. Since William et al. [28] first observed CWD in a captive deer farm in Colorado in 1967, the National Wildlife Health Center of the United States stated that CWD has been widely reported in wild and farmed deer in 35 states in the United States and 5 provinces in Canada [29]. CWD is also the only recognized transmissible spongiform encephalopathy affecting free-ranging species. In the early stage, there are no obvious symptoms, and the main clinical symptoms are progressive weight loss and significant behavioral changes such as depression and group isolation. In the late stage, it is manifested as overexcitement. Histopathologically, the lesions occur in the gray matter of the central nervous system, with bilateral symmetry and a distinct sponge-like appearance. Vacuolation around neurons and neuronal processes, astrocyte hyperplasia and hypertrophy. The most obvious lesions under the microscope are in the diencephalon, olfactory cortex, and medullary nucleus, especially the dorsal vagus nerve nucleus. Mild lesions are widely distributed in the brain and spinal cord, while there are no lesions in the basal ganglia, cerebral cortex, and hippocampus [30]. Although PrPsc can be detected in areas of the brain without sponge-like changes through immunohistochemistry (IHC) and immunoblotting, its deposition is still associated with sponge-like appearances [31]. CWD is the most contagious animal prion disease, which can be transmitted through direct contact between animals. Researchers have detected that PrPsc in CWD accumulates in saliva, urine, feces, skeletal muscle, and blood [32–34], showing highly significant horizontal transmission. Environmental factors are also likely to be involved in its transmission. A large number of studies have also confirmed the vertical propagation of CWD [35,36]. Under experimental conditions, CWD has been spread to some animals such as ferrets, raccoons, minks, and cattle (Fig. 1). However, there is currently no epidemiological research indicating a link between CWD and human prion diseases, and no new human prion diseases have been discovered in North America. Vaccination of CWD-infected brain isolates into transgenic mice expressing human PrP also showed no evidence of transmission [37].

3.4. Creutzfeldt-jakob disease

CJD is a rare, fatal, rapidly progressive human neurodegenerative disease. In 1985, Bendheim et al. [38] demonstrated that the molecular and biological properties of Creutzfeldt-Jakob preparations were sufficiently similar to scrapie prion proteins that CJD should be classified as a prion disease. The disease has four forms: sporadic CJD (sCJD), familial hereditary CJD (fCJD), iatrogenic CJD (iCJD), and variant CJD (vCJD). Although there is some variation in the clinical presentation and pathological features of different types of CJD, its neuropathological manifestations are characterised by prion protein (PrP) deposition, spongy changes in the brain, astrocyte proliferation, and neuronal loss [39,40]. where most iCJD is due to injections of human growth hormone (hGH) and dural grafts obtained from human cadavers, with a few cases caused by electroencephalography (EEG), neurosurgery, corneal transplantation, etc. The National Institutes of Health in the United States successfully transmitted tissue preparations from 8 iCJD patients to non-human primates [41]. So far, with strict disinfection of surgical instruments and biological products, the risk of iCJD has become extremely small. vCJD was the result of BSE virus transmission through food, and it was later discovered that vCJD could be transmitted through blood transfusions (Fig. 1). As of 2021, 232 cases of vCJD have been reported globally, with 178 cases in the UK and 28 cases in France. The last confirmed case of vCJD with neuropathology was a 24-year-old female from France in 2017, who was diagnosed seven and a half years after an accident in a prion biology laboratory [42]. In 1966, Gibbs et al. [43] inoculated brain biopsy materials from patients with CJD into chimpanzees. Thirteen months later, the chimpanzees showed signs of neurological disorders, with histopathological examination showing spongiform encephalopathy, confirming the infectivity of CJD. Subsequently, CJD was also transmitted to other animals. Tateishi et al. [44] inoculated tissues extracted from 10 patients with CJD into various small rodents and primates. The experiments showed pathological changes in mice, *Rattus norvegicus*, *Cricetinae*, *Meriones unguiculatus*, *Cavia porcellus*, and monkeys, but the clinical and pathological characteristics of different animals were varied. Research has shown that the brain tissue of fCJD can also transmit spongiform encephalopathy to animals. The UK Transfusion Medicine Epidemiology Review (TMER) study has found three cases of symptomatic transfusion-transmitted vCJD in the UK and one case of asymptomatic transmission (a post-mortem examination confirmed the deposit of PrPsc in the spleen), indicating the presence of blood transmission of vCJD [45,46] (Fig. 1). Since then, there have been concerns about a similar risk of transmission for classical CJD, and studies have shown that although prions have been recorded in the blood of some patients with sCJD, no cases of transfusion transmission have been found. The latest retrospective study of blood donors with CJD in the United States over the past 28 years showed that no cases of CJD have been found in the treated population [47], and the risk of blood product transmission of classic CJD was extremely low, still theoretically existing. Kamin and Patten [48] reported four patients who had eaten wild goat and squirrel brains, one of whom had a definite diagnosis of CJD, and three of whom had probable CJD without an autopsy but with clinical signs of CJD. Gibbs et al. [49] fed the brain, kidney, and spleen tissue from chimpanzees infected with Creutzfeldt-Jakob virus to squirrel monkeys, which developed spongiform encephalopathy after an asymptomatic incubation period of 23 and 27 months, respectively, and the disease was indistinguishable from those of squirrel monkeys vaccinated with CJD via intracerebral or peripheral pathways. These studies warn that the oral transmission of CJD cannot be ignored.

3.5. Kuru

Kuru is an epidemic that first broke out in the Fore tribe of Papua New Guinea. It is the first human prion disease to be identified and is associated with a D178 mutation in the PRNP gene. It was first reported to the Western medical community in 1957 by Gajdusek and Zigas [50]. Kuru can cause fatal cerebellar ataxia, accompanied by tremors, dancing, and motor disorders. The significant neuropathological feature

of Kuru is the presence of many amyloid plaques, later known as "Kuru plaques" discovered in Beck et al.'s study cases [51,52]. Kuru plaques are mainly distributed in the granule cell layer of the cerebellum, basal ganglia, thalamus, and cerebral cortex. In 1960, Hadlow observed reports of Kuru plaques and pointed out that Kuru disease was similar to pruritus, and Kuru might be an infectious disease expressed after a long incubation period [53]. In the same year, Klatzo et al. [54] further pointed out that the histopathological changes of Kuru were similar to those of CJD after studying its histopathology. Due to the scarcity of resources at that time, the people of the tribe would eat the brains and bodies of the deceased. At the beginning of the 21st century, researchers noticed this ritual and for the first time linked cannibalism with kuru. In 1963, Gajdusek et al. [55] first inoculated dissected Kuru brain suspension into chimpanzee brains, within less than three years, these animals developed progressive neurological disorders, and autopsy reports found histopathological changes similar to Kuru patients and visible in scrapie patients in chimpanzees. Subsequently, it was demonstrated that Kuru can be transmitted to non-primates such as goats, sheep, guinea pigs, domestic cats, gerbils, ferrets, and minks, as well as to non-human primates including rhesus monkeys, marmosets, gibbons, black mangabeys, macaques, and cynomolgus monkeys [56] (Fig. 1). Kuru is considered a transmissible disease like scrapie. The most obvious source of kuru is cannibalism in religious rituals, which has disappeared with the decline of rituals. An experiment feeding known to be infected with prions to squirrel monkeys showed that a squirrel monkey fed 70.5 g of the brain, kidney, and spleen tissue from a chimpanzee infected with the kuru virus developed spongiform encephalopathy after a 36-month asymptomatic incubation period. After death, typical experimental kuru pathological changes appeared in the brain [49], indicating that kuru can be transmitted through the oral cavity.

3.6. Fatal familial insomnia

FFI is an autosomal dominant prion disease that selectively damages the limbic system of the cerebral cortex, and one of its main features is sleep deprivation. In 1986, Lugaresi et al. [57] reported the first case of FFI, which came from an Italian family with multiple members suffering from the same progressive neurological disorder. The clinical manifestations of this disease are inattention, sleep deprivation, autonomic dysfunction, and ataxia, with pathological changes limited to the thalamus. The histopathological features are the loss of thalamic neurons and proliferation of astrocytes, with the anterior ventral area (AV) and dorsal medial nucleus (MD) of the thalamus being the most severely and persistently affected brain regions [58]. Genetically, FFI is associated with missense mutations at codon 178 of the PRNP gene and methionine at codon 129 of the polypeptide. People once had doubts about the infectivity of FFI because experiments to spread FFI to non-human primates, including 18 non-human primates, had failed. It was not until 1995 that Tateishi et al. [59] reported the first successful transmission of FFI to experimental animals by injecting tissue fluid made from FFI thalamic homogenates into mice. Since then, Collinge et al. [60] inoculated the brain homogenates from two FFI patients into transgenic mice expressing human PrP. The mice developed rapidly progressing neurological syndromes, confirming the infectivity of FFI.

3.7. Gerstmann-Straussler syndrome

GSS is a genetic prion disease caused by a series of mutations within the open reading frame of the PRNP on chromosome 20. Originally described in a large Austrian family with autosomal dominant inheritance. The typical pathological feature of GSS is the presence of extensive multi center amyloid plaques, which can be selectively immunostained by PrP antibodies. The 102 codon point mutation in PRNP causing proline (CCG) to be replaced by leucine (CTG) is the first genetic defect discovered in GSS disease, and is the most common one [61]. It has been confirmed that the disease can be successfully transmitted to nonprimates by inoculating the brain homogenate of GSS patients [62].

4. Pathogenesis and infection pathways of prion diseases

4.1. Pathogenesis

Conversion of the prion protein from the normal cellular isoform PrPc conformation to the abnormally folded amyloid isoform PrPsc, which ultimately leads to the accumulation of PrPsc is a key causative agent of prion diseases. PrPsc can be specifically detected in prion-infected tissues or cells, including follicular dendritic cells of the central nervous system, especially neurons, and lymphoreticular system. In contrast to PrPc, PrPsc is enriched in β-sheet structures, highly detergent insoluble, resistant to protease degradation, and readily assembles into amyloidogenic fibrils called prion rods [63]. Images of PrPsc rods have been visualised by atomic force and cryo-electron microscopy, demonstrating that misfolded PrPsc can be aggregated into repetitive double-helical fibrils in the form of rods [64]. In prion diseases, the conformational variation in PrPsc produces different patterns of PrP accumulation regions, resulting in different disease phenotypes. Notably, aberrant folding and aggregation of PrPsc is not only a central feature of the pathology, but also a key initiator driving disease progression. It has been shown that PrPsc can interfere with the ubiquitin/proteasome system in the early state of the disease, leading to impaired function of this protein degradation pathway, thereby enhancing PrPsc accumulation [65]. The accumulation of these pathological proteins does not exist in isolation - their conformational changes activate microglia, leading to neuroinflammation, which results in continued activation of the immune response within the CNS, secretion of pro-inflammatory cytokines such as TNF-α and IL-1β by microglia, and excessive synaptic pruning, leading to neuronal dysfunction and degeneration [66]. At the same time, the microglia also interact with other CNS cells such as astrocytes and neurons, creating a signalling cascade that amplifies neuroinflammation, leading to a shift from neuroprotective function to neurotoxic outcome. In addition, PrPsc aggregates can trigger reactive oxygen species (ROS) overproduction by disrupting the function of the mitochondrial electron transport chain, which coupled with the production of ROS by microglia and astrocytes during inflammatory stimuli, can lead to mitochondrial dysfunction, lipid peroxidation, and neuronal death [67]. It is important to note that oxidative stress exacerbates neuroinflammatory signalling, thus creating a vicious cycle that accelerates disease progression. It is evident that prion disease is a dynamic process starting with protein misfolding and multiple pathological processes that are intertwined and synergistically advanced.

Experiments have shown that PrPc knockout mice (Prnpo/o) are resistant to prion infection, and inoculation of prions in the brain does not cause morbidity nor transmission [68]; transgenic reintroduction of PRNP restores pathogenesis and infectiousness in Prnpo/o mice [69]. It is evident that protein misfolding and aggregation play a crucial role in the development of prion diseases, and we will also focus on this mechanism. In addition, it has been reported that depletion of endogenous PrPc in infected mice reverses early spongy changes and prevents neuronal loss and clinical disease progression [70]. A growing body of research suggests that there is a polymerization mechanism of PrPsc that forms a seed or template that continuously spreads and propagates in the body, forming amyloid fibrils that cause disease [71] (Fig. 2). In addition to self propagating within cells, prions can also spread within or between individuals. Kocisko et al. [72] produced PRPsc-like protease K resistant biological PrP, and developed a protein misfolding cycle amplification technique (PMCA), successfully amplified PRPsc-like PrP *in vitro*, and eventually enriched PrPsc converted from PrPc. Subsequent studies showed that the resulting PrPsc was infectious [73]. The oligomeric intermediates formed during protein misfolding are increasingly recognized as the main pathogenic factors of diseases, and these

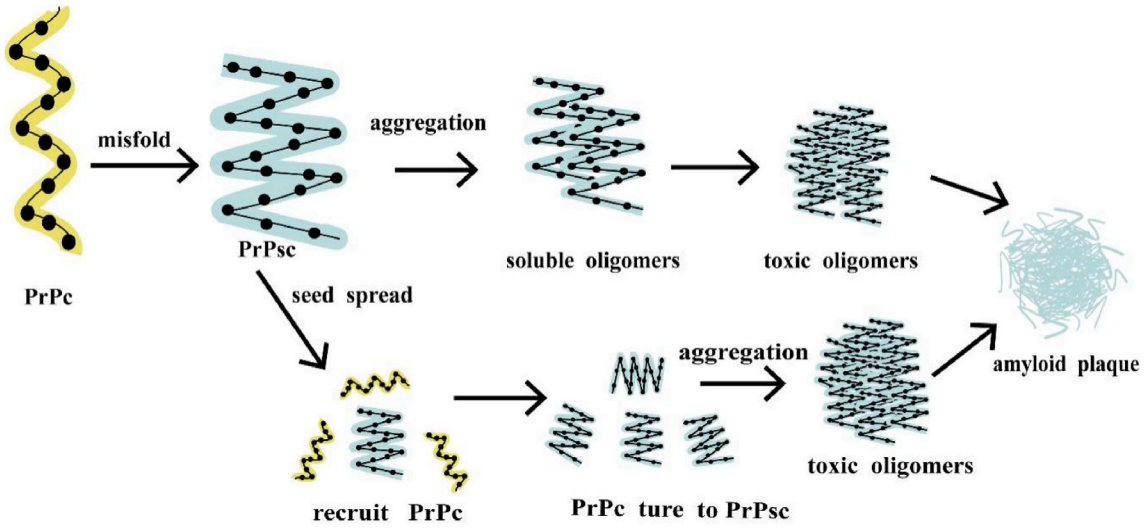

Fig. 2. The aggregation mechanism of misfolded protein (PrP). Initially, the normal PrPc molecule contains more α-helices (indicated in yellow in the figure), and after misfolding, undergoes a conformational change into β-sheet-rich PrPsc (indicated in blue in the figure) [76]. PrPc and PrPsc are heterodimers, and the primary structure of the protein is not altered. prPsc not only aggregates itself to form soluble oligomers, but also acts as a "seed" recruits more normal form of PrPc, induces them to undergo the same conformational change, and further aggregates into toxic oligomers to form amyloid.

oligomers are closely related to neuronal dysfunction and cell death [74]. In addition, there is evidence to suggest that amyloid toxicity is also caused by oligomers forming amyloid pores on the cell membrane. It is believed that soluble oligomers can interact with the cell membrane to produce so-called "amyloid pores" that exhibit structural and functional properties similar to pore-forming toxins, disrupting the cell membrane, leading to ion imbalance, small molecule, and even protein entry and exit, affecting cell signalling pathways and fate [75].

4.2. *Infection pathways*

Prion diseases are classified as sporadic (85 %), hereditary (10–15 %), and acquired (<1 %) diseases. Sporadic prion diseases are dominated by sCJD, hereditary prion diseases include GSS, FFI, and fCJD, all inherited as a result of autosomal dominant mutations in the PRNP gene. Acquired prion diseases are caused by exogenous transmission of PrP, such as Kuru and vCJD. Experimental studies conducted by the National Institutes of Health in the United States have shown that the overall transmission rates of all types of prion diseases in non-human primates were 87 % (291/335), with iCJD, Kulu, and sCJD transmission rates reaching 90 % or higher, while the transmission rate of hereditary prion diseases was 68 % [42]. Based on existing research, we have summarized the possible infection routes of prion transmission: ①Prion enters the digestive tract of the body together with food and water during ingestion, especially after entering the intestine, it enters the brain through the retrograde transport of nerve fiber axons in the brain-gut axis. The most direct evidence is that people are infected with vCJD by eating beef contaminated with BSE. In addition, recombinant mouse PrPsc with high infectivity can infect mice with prion diseases through foodborne transmission, and the resulting symptoms and pathological biochemical characteristics are characteristic changes of prion diseases. However, the incubation period of foodborne transmission is longer and the infection rate is lower, with significant individual differences among animals. However, once ingested, even if the disease cannot be successfully caused by infection, there are still low levels of pathogenic prions in the body. And an increasing number of studies have shown that the human gut microbiota plays an important role in regulating the brain's physiological functions (through immune, neural, endocrine, and metabolic pathways) and maintaining homeostasis in the internal environment [77]. ②Prion enters the lungs through the respiratory system, enters the capillaries through the alveoli and respiratory membranes (or through the skin mucosa, sensory mucosa, and body fluids), is transported to the head through the blood circulation, and then enters the brain through the blood-brain barrier or the blood-cerebrospinal fluid barrier. The four cases of vCJD transmission through blood transfusion mentioned earlier can serve as evidence of this infection pathway. Another report of subclinical hematogenous vCJD infection indicated that the transmission of BSE to humans enhanced its toxicity and expanded the range of susceptible individuals [78]. In addition, researchers found PrPsc in the spleen and muscle tissue of sCJD patients, and confirmed the infectivity of prions in the muscle, blood, and saliva of deer with CWD. In addition to self propagating within cells, prions can also spread within and between individuals. Several transmission mechanisms have been reported in cells, including the release of extracellular vesicles and uptake by recipient cells, as well as tunnel nanotubes connecting donor and recipient cells [79–81].

5. Abnormal proteins in common neurodegenerative diseases

Neurodegenerative diseases (NDs) are a highly destructive class of diseases that affect human movement, sensation, cognition, and memory, etc. Common ones include Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), chronic traumatic encephalopathy (CTE), etc. A hallmark feature of this type of disease is the misfolding and aggregation of abnormal proteins in the nervous system, leading to dysfunction of nerve cells, loss of synaptic connections, and brain damage. For example, β - amyloid (Aβ), tau protein, α-synuclein (α-syn), interacting DNA binding protein kAa43 (TDP-43), etc. Although these protein aggregates have different structures and functions, all neurodegenerative diseases typically exhibit changes in their conformation and aggregation. More and more evidence suggests that these misfolded abnormal proteins can spread *in vivo* and *in vitro* through a prion-like mechanism, inducing the formation of misfolded protein aggregates such as amyloid plaques and neurofibrillary tangles. The causative proteins, symptoms, pathological features and locations of the above several neurodegenerative diseases can be found in Table 1. Currently, neurodegenerative diseases including AD and PD are increasingly referred to as "prion-like" diseases [82]. The unique infectivity of prion diseases has raised concerns about whether these neurodegenerative diseases have some potential infectivity, but there is currently a lack of epidemiological evidence. However, recent reports of

Table 1
Neurodegenerative diseases: proteins and pathology.

Disease	Pathogenic protein	Characteristic symptoms	Pathological features	Main position	References
Prion disease	Prion protein	Behavioral abnormalities and ataxia (animal). Cognitive impairment and ataxia (human).	Neuronal damage or even loss, glial cell proliferation, aggregation and precipitation of different sizes of prion proteins.	Cerebral cortex, thalamus, basal nucleus, brain stem, etc.	[1,2,16,40,52]
Alzheimer' s disease (AD)	Aβ,tau	Progressive cognitive impairment and memory loss.	Extracellular aggregation of Aβ in the cerebral cortex and peripheral regions and intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein.	Hippocampal zone, temporal, parietal lobes and frontal cortex.	[3,83]
Parkinson' s disease (PD)	A-synuclein	Tremors, muscle rigidity, bradykinesia, and ataxia.	Loss of dopaminergic neurons in substantia nigra,α-syn aggregates to form internal inclusion bodies.	Midbrain substantia nigra and cerebral cortex.	[84–86]
Amyotrophic lateral Sclerosis (ALS)	TDP-43, SOD1, FUS	Muscle spasms, weakness, atrophy, and loss of motor neuron function.	TDP-43 abnormally aggregated into inclusion bodies.	Motor cortex, brain stem, spinal cord.	[87,88]
Chronic traumatic encephalopathy (CTE)	Tau,TDP-43	Mood disorders, behavioral impulse, cognitive frailty, motor disorders	Hyperphosphorylated Tau is deposited in perivascular and superficial cortical areas as neurofibrillary tangles.	Subcortical, perivascular, and periventricular areas in the frontal and temporallobes.	[89–91]

unintentional transmission of Aβ cases through medical and surgical procedures have heightened concerns about the possibility of these misfolded abnormal proteins spreading between individuals as rare events and with long incubation periods. The following will focus on abnormal aggregated proteins in neurodegenerative diseases, revealing their infectiousness.

5.1. Aβ

Aβ is produced by a series of enzymatic degradation of amyloid precursor protein (APP). Under normal physiological conditions, the production and degradation of Aβ can maintain a balance. In pathological conditions, Aβ aggregates to form insoluble amyloid protein rich in beta sheets, which accumulates in the brain tissue to form amyloid plaques. Senile plaques (SP) formed by Aβ deposition have been demonstrated to be the main component of amyloid plaques in the brain tissue of AD patients. Amyloid substances of Aβ can also cause a common cerebellar vascular disease-cerebral amyloid angiopathy (CAA), which is considered a pathological feature of most AD patients but can also independently manifest as cerebral hemorrhage [92]. The aggregation of Aβ has a seed transmission mechanism similar to that of prions, which can spread in the brain. Studies have shown that the deposition of Aβ in AD patients follows five different stages: 1. Aβ deposition only exists in the neocortex; 2. Spread to the hippocampus; 3. Aβ deposition is found in the amygdala, thalamus, and striatum; 4. Some areas of the brainstem and substantia nigra are filled with Aβ deposits; 5. There are also Aβ deposits in the cerebellum [93,94]. Harper et al. [95] demonstrated through *in vitro* studies that Aβ seeds rich in β-sheets can effectively induce Aβ monomers to obtain β-sheets and assemble into amyloid-like proteins. Some *in vivo* experiments also support this mechanism. For example, inoculating the brain homogenates containing Aβ aggregates into susceptible transgenic mice accelerated the deposition of Aβ, which could self-propagate [96]. Injecting the brain extracts rich in Aβ into the hippocampus could locally induce Aβ deposition. Once pathology occurred, Aβ deposition selectively spread to the axial connections of the brain [97]. *In vitro* experiments also support that Aβ aggregates can propagate through axons. The homogenate of AD patients was injected into the brains of marmosets and Aβ deposition was induced 6–7 years later [98], injecting artificially assembled Aβ aggregates into young transgenic mice also produced Aβ. The successful transmission of AD cases was also achieved through peripheral (intraperitoneal injection) inoculation of AD brain extract into APP23 transgenic mice, indicating that Aβ seeds could be transported from the periphery to the brain [99]. As early as 2015, evidence of human-to-human transmission of Aβ pathology was reported. In an autopsy study of 8 iCJD patients, moderated to severe Aβ lesions in gray matter and blood vessels were found in 4 patients, and sparse Aβ deposits were found in 2 other patients, none of whom had disease-causing gene mutations associated with other AD, and Aβ deposits in their gray matter and blood vessel walls were typical features of AD and CAA, respectively. This indicates that healthy individuals exposed to c-hGH are at risk of iatrogenic infection of CAA, and suggests that if c-hGH recipients do not die from iCJD, they may eventually develop AD [100]. Between 2017 and 2022, Banerjee et al. [101] found 8 recipients in cases treated with c-hGH prepared by the HWP method, 5 of whom met the diagnostic criteria of the National Institute on Aging and the Alzheimer's Association (NIA-AA) for AD. The other 3 patients (1 patient had symptoms that met the criteria for NIA-AA mild cognitive impairment, 1 case only had subjective cognitive symptoms, and 1 case was asymptomatic), excluding genetic factors, coupled with the relatively young age of the patients not consistent with sporadic AD, which they believed to be the result of transmission of Aβ after receiving contaminated c-hGH in childhood, i.e., iatrogenic Alzheimer's disease (Fig. 1), suggesting that AD should be considered a potentially contagious disease. Greater attention needs to be paid to its impact on public health and to ensure the control of surgical instruments.

In recent years, Aβ has also been shown to be a predisposing factor for stroke, with irregular clearance of Aβ leading to damage to the blood-brain barrier and neuroinflammation occurring, allowing insufficient blood supply to the brain to cause stroke, and elevated levels of Aβ have been found in patients suffering from acute stroke events [102]. In stroke, the accumulation of Aβ is secondary to pathological changes, and there is no clear evidence that Aβ has the prion-like behaviour of AD in stroke. However, both stroke and AD involve abnormal accumulation of Aβ, neuroinflammation, and blood-brain barrier damage, and there are similar pathological mechanisms. The intersection of the two in Aβ pathogenesis may be a mutual risk factor, and future studies should focus on the common pathological mechanisms and therapeutic strategies for both.

5.2. Tau

Tau protein is a microtubule-associated protein expressed by the MAPT gene, which binds to microtubules (MTS) and promotes their assembly and stabilization of proteins. Tau protein can produce six major tau subtypes through selective RNA splicing, all of which can be expressed in central nervous system neurons of healthy adult brains [103]. The formation of neurofibrillary tangles (NFTs) within neurons caused by tau protein misfolding and hyperphosphorylation is a hallmark of AD pathology. NFTs is also a pathological feature of CTE, with hyperphosphorylated tau protein (p-tau) deposited as NFTs in perivascular and superficial cortical areas [89]. In addition, tau protein accumulation has also been observed in some other neurodegenerative diseases, such as frontotemporal dementia (FLTD), progressive

supranuclear palsy (PSP), cortical basal degeneration (CBD), Pick's disease, and PD patients. The tau deposits in AD patients are mainly limited to the olfactory and hippocampal formation areas in the early stages of the disease, but are widely found in the neocortex area in the late stages [104]. A study has shown that tau protein could be released into the extracellular space through membrane vesicles after neuronal death, and interacted with specific cell receptors to produce toxicity to surrounding cells [105]. Clavaguera et al. [106] found in experimental transmission of tau protein in a mouse model that injecting the tau protein extracted from the brains of mice expressing P301S mutant tau protein into individual mice overexpressing tau protein could induce the aggregation and diffusion of wild-type tau protein. And injecting tau fibrils polymerized under heparin into the brains of P301S mutant mouse strains could induce pathological induction and diffusion of tau. In addition, tau protein isolated from the brains of tau patients was also able to induce tau expression in wild mice. Injecting a small amount of tau protein seeds into the brains of transgenic mice expressing human tau protein could induce excessive phosphorylation and accumulation of tau protein [107], while the induction degree of wild-type mice was lower. Moreover, this exogenous-induced disease would spread from the injection site to the brain regions connected by axons. In 2014, Clavaguera et al. [108] first reported that intraperitoneal injection of tau seeds could induce tau protein disease in transgenic mice, and tau seeds could reach the central nervous system from the periphery. It can be seen that the aggregation and transmission of tau proteins are similar to those of prions. Pathogenic misfolded tau proteins can act as "seeds" to recruit endogenous tau proteins to form larger abnormal conformations and slowly spread in interconnected brain regions.

NFTs in AD and CTE are both composed of p-tau, but differ significantly in distribution patterns and morphology. A large body of evidence has now confirmed the prion-like behaviour of tau proteins in AD, capable of propagating and spreading. CTE is a neurodegenerative disorder associated with repetitive head trauma, and is commonly seen in athletic and military populations. Although the clinical and neuropathological manifestations of CTE suggest that CTE and AD are distinctly different entities, a large number of studies have demonstrated a correlation, and CTE appears to be a risk factor for AD, capable of increasing or facilitating the development of AD, and deserving of further attention. Turner et al. [109] also provided a case of overlap between AD and CTE, suggesting the possibility that a single individual might have both neuropathological features that was also a form of cross-transmission.

5.3. α-syn

α-syn is a presynaptic neuronal protein that plays a crucial role in PD and other synucleinopathies, including dementia with Lewy bodies (DLB) and multiple system atrophy (MSA). Numerous studies have shown that the misfolding and aggregation of α-syn are the major pathogenic event in PD, and that these aggregates, which are located at the presynaptic level and impair axonal transport, can lead to neuronal damage in the substantia nigra compacta and affect dopaminergic denervation of the striatum [84]. Although the majority of PDs are of the disseminated type, missense mutations and proliferation of the α-synuclein protein gene (*SNCA*) can lead to familial PDs with an autosomal dominant inheritance [110]. Under normal physiological conditions, α-syn is a soluble protein that can regulate the release of vesicles. Point mutations (e.g., A53T, A30P, E64K) in the α-syn-encoding genes or an increase in gene copy number can promote α-syn misfolding and aggregation [111]. According to neuropathological observations, Braak et al. proposed that α-syn spread in a spatiotemporal manner, and LB pathology progressed from the nucleus pulposus and olfactory bulb to the neocortex [85]. Animal experiments have shown that exogenous introduction of brain-derived or synthetic α-syn seeds induced the aggregation of endogenous monomers α-syn, forming Lewy-like inclusion bodies within cells, inducing progressive neurodegenerative diseases in animals, and pathological changes propagated from the inoculation site along anatomically connected structures [112]. In rodent models, misfolded α-syn was effectively internalized by olfactory bulb neurons, then reverse transferred to functional connectivity regions, and ultimately spread to the limbic system and substantia nigra pars compacta [113]. Recasens et al. [114] injected homogenate rich in Lewy bodies extracted from the brains of PD patients into non-human primates, which could induce α-syn aggregation and lead to striatal neurodegeneration. Two patients with PD survived for a long time (11–16 years) after transplanting dopamine neurons from the midbrain of fetuses, but α-syn positive Lewy bodies formed in the transplanted neurons, providing the first evidence that the disease can spread from the host to transplanted cells [115]. Sacino et al. [116] successfully induced the central nervous system lesions by injecting α-syn seeds into the hind limb muscles of transgenic mice, demonstrating for the first time the peripheral transmission of α-syn misfolded proteins. Subsequently, Ayers et al. [117] also confirmed the ability of α-syn seeds to spread from the peripheral nervous system to the neuroanatomical regions of the central nervous system through intravenous injection. In recent years, a large amount of evidence has shown that PD may occur in the gut, and there is a link between the gut microbiota and PD. Clinically, most PD patients experience early gastrointestinal dysfunction symptoms such as constipation, changes in bowel habits, excessive saliva secretion, difficulty swallowing, and nausea, etc. Braak Hypothesis suggests that abnormal a-syn accumulates in the gut and can be transmitted to the brain through the brain-gut axis in a manner similar to that of prions [118]. Pathophysiologically, α-syn inclusion bodies have also been found in the intestinal nervous system, glossopharyngeal nerve, and vagus nerve of patients. In addition, studies have shown that vagotomy seems to have a protective effect on the subsequent development of PD [119]. Arotcarena et al. [120] injected patient-derived α-syn aggregates into the gut and striatum of non-human primates, which induced nigrostriatal lesions and pathological changes in the gut nervous system. The above research is consistent with the possible infection pathways of prion transmission that we summarized in section 3.2. This further illustrates the potential risk of misfolded α-syn entering the digestive tract and spreading PD through the brain-gut axis to the brain. Since then, studies have used allogeneic symbiosis to investigate whether synucleinopathy can be transmitted through the bloodstream between individuals in a mouse model. The results showed that within a selected time range, the disease did not spread through the bloodstream [121]. Adler et al. [122] conducted autopsies on 90 married couples, and found that 42 couples had 1 spouse with synuclein disease, and 16 couples had both spouses with synuclein disease, indicating that the transmission of synuclein disease between spouses was unlikely. So far, there is no research indicating that PD can be transmitted between individuals through iatrogenic or other pathways.

5.4. TDP-43

TDP-43 is a highly conserved DNA/RNA-binding protein, which is mainly localised in the nucleus. TDP-43 aggregates are the hallmark pathological feature of ALS [88]. TDP-43 has a C-terminal end of a low-complexity structural domain, and most of its disease-causing mutations are localised to this fragment due to its ability to increase prion-like properties, trigger aggregation, and produce toxicity [123]. Smethurst et al. [124] demonstrated that insoluble phosphorylated TDP-43 from the brain and spinal cord of ALS patients could exhibit seed aggregation *in vitro*, forming TDP-43 inclusion bodies. Feiler et al. [125] have confirmed that TDP-43 oligomers could diffuse between cells at the end of axons, and these oligomers could further aggregate as seeds in absorbing cells. Ding et al. [126] research has shown that TDP-43 aggregates could be transferred between cells through tunnel nanotubes (TNT). Several laboratory studies have shown that exosomes are also a mode of prion-like TDP-43 transmission between cells, and are involved in the secretion and transmission of TDP-43 aggregates [127]. It is clear

that ALS has the characteristics of a prion-like disease, and the misfolding and aggregation of TDP-43 protein play a crucial role in the progression of the disease. Recently, Tamaki et al. [128] used induced pluripotent stem cells (iPSCs) derived the brain organoids as receptor central nervous system tissue models, which were equivalent to anatomical human brains. They injected protein extracts containing pathogenic TDP-43 into the brain organoids, and the study showed that pathological changes gradually spread in the organoids in a time-dependent manner, and also caused astrocyte proliferation, indicating that the pathogenic TDP-43 of ALS can act as seeds and spread in simulated human central nervous system tissues. However, there is currently no research showing that misfolded TDP-43 can spread between individuals.

Taken together, the pathological manifestations and distribution patterns of these aberrant proteins vary across diseases, but their common prion-like behaviour provides new insights into the mechanisms of transmission of neurodegenerative diseases. AD is the most common degenerative disease of the central nervous system with progressive cognitive deficits and memory impairment, and sporadic AD is known to be the most common type of AD, and apolipoprotein E (APOE) is considered the strongest risk factor for sporadic AD, especially the APOE4 allele, which increases the risk of developing AD. It is estimated that 50 % of sporadic AD is caused by the AOPE4 allele [125]. In addition, environmental factors also play an important role in sporadic AD disease, such as long-term exposure to toxic substances, smoking, air pollution, etc., which are also related to the onset of AD [126,127]. Research has shown that gene mutations in *APP*, presenilin 1 (*PSEN1*), and presenilin 2 (*PSEN2*) can lead to overproduction or the formation of an abnormal form of Aβ, which is believed to be the cause of hereditary AD, accounting for approximately 1 % of AD [128]. Banerjee has also demonstrated the existence of iatrogenic AD, indicating that similar to CJD, AD has three different forms: sporadic, genetic, and iatrogenic. AD should be considered a potentially infectious disease, which further emphasises its importance in public health. Although similar medical transmission has not been demonstrated in other neurodegenerative diseases, the transmissibility of abnormal proteins exists, and future studies should continue to explore the mechanisms of transmission of these abnormal proteins, and their role in disease progression to provide new strategies for the early diagnosis and treatment of neurodegenerative diseases.

6. Discussion

6.1. Similarities between abnormal proteins and prions in neurodegenerative diseases and therapeutic strategies

The prion that causes prion diseases is not a real virus, but rather a protein infectious particle that does not contain nucleic acid, but has similar characteristics to viruses and can self-transmit. Research has found that the misfolded conformations of Aβ, tau, a-syn, and TDP-43 are also rich in beta sheets similar to those in PrPsc structure, making them prone to form intermediate oligomers and higher-order fiber aggregates [129,130]. In prion diseases, oligomers, the intermediates formed by PrPsc aggregation, are considered to be the most infectious [131]. Similarly, a large amount of evidence suggests that intermediate-oligomers formed by abnormal protein misfolding in neurodegenerative diseases, seem to be the true culprits of the disease and can produce cytotoxicity [132,133]. Jarrett et al. [134] used a seed nucleation model to describe the mechanism of misfolding and aggregation of aberrant proteins, and their results showed that it is also very similar to the prion seed propagation mechanism (Fig. 2). Therefore, inhibiting the misfolding of proteins and preventing them from shifting to the wrong conformation rich in β-sheets; preventing the formation of oligomers; facilitating the removal of abnormal proteins; and blocking the seeding and propagation of proteins are some of the effective strategies for the treatment of neurodegenerative diseases. There are also related studies that have made some progress, for example, Aducanumab is a monoclonal antibody against Aβ, whose main mechanism of action is to slow down the pathological progression of AD by targeting and removing oligomers and plaques of Aβ [135]. A compound known as the CLR01 molecular clamp, which inhibits the aggregation of various amyloid proteins and promotes their clearance, has also shown great potential in the treatment of neurodegenerative diseases [136]. Activation of autophagy, an important intracellular degradation mechanism, has also shown therapeutic potential in neurodegenerative diseases. However, autophagy has a two-sided nature, e.g., in multiple sclerosis (MS), overactivation of autophagy may exacerbate neuroinflammation and pathological damage [137]. Therefore, the regulation of autophagy needs to be precisely balanced to achieve its protective effects and avoid potential harm. There are also a number of therapeutic strategies to address the mechanisms of neuroinflammation and oxidative stress induced by misfolded aggregated proteins [138]. For example, tatin analogues can exert neuroprotective effects by inhibiting inflammation and oxidative stress disorders, and improving neuronal signalling pathways; the antioxidant effect of uric acid attenuates oxidative stress-induced neurodegeneration in AD and PD, but high uric acid carries certain risks [139]. In recent years, the ketogenic diet (KD) has also attracted attention in the treatment of AD. KD attenuates the pathological progression of AD by reducing oxidative stress, mitochondrial dysfunction, and enhancing autophagy, but its strict dietary restriction is difficult to adhere to for a long period of time and is subject to individual variations [140]. It can be seen that the current therapeutic drugs and methods for neurodegenerative diseases mainly focus on relieving symptoms and delaying disease progression, which have certain limitations and are not yet able to cure the disease completely. Future research should focus on developing more specific drugs and exploring the possibility of early intervention. In addition, although there is a lack of evidence of individual transmission of misfolded proteins other than iatrogenic transmission of Aβ, precautions have to be strengthened, especially as more and more PD patients are undergoing neurosurgery to implant deep brain stimulation electrodes.

6.2. Cross-transmission in neurodegenerative diseases

In recent years, research has shown that there is cross-propagation of misfolded proteins between NDs, and there may be two or more protein aggregates in different NDs. A typical example is the AD mentioned above, which exhibits both intracellular tau neurofibrillary tangles and extracellular Aβ-amyloid plaques. Experimental evidence showed that aggregated Aβ could induce tau protein lesions in mice and promote the spread of tau protein disease [141]. The indirect or direct connection between Aβ and tau protein has also been reported, and it has been suggested that Aβ oligomers may provide seeds for the initial formation of tau oligomers, which can then undergo self-replication and transmission [142]. Tau can also interact with α-syn and co-locate in Lewy bodies. Xiang et al. [143] showed through mouse models that the common pathological changes of tau and α-syn could spread from the gut to the brain and cause behavioral disorders. There is cross-propagation of multiple erroneous proteins in the same ALS. In addition to TDP-43 aggregation, superoxide dismutase 1 (SOD1) and fusion protein (FUS) have been found in a few ALS inclusion bodies. Studies have shown that both could form amyloid-like fibrils *in vitro* and act in a prion-like manner [144,145]. In addition, researchers have also discovered PrPc in AD and PD patients, and studies have shown that PrPc may act as receptors/sensors for different protein aggregates, regulating neuronal toxicity and disease transmission [146]. For example, interactions between PrPc and Aβ enhance the toxicity of Aβ [147] and interactions with tau aggregates promote its internalisation [148]; interactions with TDP-43 increase the uptake of TDP-43 protofibrils and modulate toxicity [149]; and interactions with a-syn modulate its internalisation and act as a mediator of the neuronal damage induced by a-syn oligomers [150]. Polido et al. [151] provided evidence

for the presence of TDP-43 aggregates in transgenic Drosophila expressing mammalian PrP and in neurons from patients with Creutzfeldt-Jakob disease. Furthermore, in addition to cross-seeding of misfolded proteins, there is also cross-seeding between different NDs, such as the above mentioned stroke and CTE which both correlate with AD and increase or exacerbate the occurrence of AD. Cross-seeding of misfolded proteins and cross-cutting between NDs increase the complexity of the pathogenesis of NDs, but it also opens up new possibilities for further understanding of NDs and treatment.

6.3. Discussion on disease susceptibility

Research on prion diseases has found that different species have varying susceptibility to prions, as well as differences in incubation periods. The base changes in the PRNP sequence of the PrP encoding gene, i.e. the polymorphism of PRNP, have an impact on the susceptibility of prions. For example, sheep and goats with different PRNP genotypes have varying susceptibility and latency to scrapie pathogens. Numerous studies have shown that different combinations of methionine (M) or leucine (V) at codon 129 have varying sensitivities to prion diseases. There are very few 129M/V heterozygotes in sCJD patients. A study of clinical vCJD cases undergoing genetic analysis found that all 129 genotypes were 129M/M homozygotes, suggesting that other genotypes might have resistance to BSE infection. In addition, patients with iatrogenic CJD caused by human growth hormone (hGH) have different genotypes of 129 in different regions. In the United States and France, the proportion of 129M/V heterozygotes is relatively low, and the incubation period of patients is longer than that of homozygous patients; The proportion of 129M/M homozygotes decreased in relevant patients in the UK [152]. The proportion of 129M/M and V/V is higher in Kuru patients, and the heterozygosity during the disease epidemic is higher in the unaffected population [153]. Therefore, we speculate that neurodegenerative diseases similar to prion diseases also have differences in susceptibility among different species. As early as 2005, a report showed that the proportion of the M allele at codon 129 of the PRNP gene in AD patients was too high. Subsequently, a large-scale analysis of more than 4000 AD patients and a control group showed that the statistical risk of AD was higher in MM homozygotes [154]. A recent case-control study conducted by Liu et al. [155] in the hospital also showed that the polymorphisms at the rs243866 and rs243865 loci of the matrix metalloproteinase 2 (*MMP-2*) gene were closely related to the age of onset of AD. The *rs2*43866AA genotype may be risk factors for predisposing to AD. Therefore, further exploration is warranted in the study of susceptibility to neurodegenerative diseases, which can also provide new directions for their treatment.

6.4. Some unknown or prion-like protein virus

With the increasing number of global depression patients, research teams abroad have pointed the finger of depression at viruses, such as finding a significant connection between human herpesvirus 6 (HHV-6) and psychiatric disorders. The pathogen of HHV-6 may disrupt neural development during critical developmental stages of early life, and interfere with the immune system. Studies have also shown that these human herpesviruses may cause other neurological disorders, such as Alzheimer's disease and medial temporal lobe epilepsy. Harberts et al. [156] have shown that HHV-6 could lurk and store in the nasal cavity, supporting HHV-6's use of the olfactory pathway to enter the central nervous system. In addition, data suggests that HHV-6 can establish infection in human olfactory ensheathing cells (OECs) *in vitro*, and infected OECs exhibit active viral replication. Kobayashi et al. [157] identified an HHV-6B latent protein, SITH-1, that was specifically expressed in astrocytes. Through a mouse model, they found that SITH-1 promoted apoptosis of astrocytes in the olfactory bulb, and mice exhibited overactivation of the hypothalamic pituitary adrenal (HPA) axis and depressive symptoms, indicating that the protein produced by the HHV-6 virus (SITH-1 protein) may contribute to the occurrence of depression. Boyko et al. [158] established a unique animal model of depression contagion by co-living healthy rats with chronic unpredictable stress (CUS)-induced depressed rats for five weeks, and found that the healthy rats exhibited depressive symptoms. The transmissibility of depression among animals, coupled with the high incidence trend of depression in recent years, is worth pondering whether there is some unknown or prion-like protein virus that makes depression contagious. In addition, there is currently ample evidence to suggest that coagulation disorders involving fibrin clots are the main cause of sepsis, systemic inflammatory response syndrome (SIRS), septic shock, multiple organ dysfunction syndrome (MODS), and disseminated intravascular coagulation (DIC). Kell et al. [159] showed that this fibrin was essentially an amyloid protein, lipopolysaccharide (LPS) was shown to cause this abnormal form of fibrin, and suggested that there was some kind of autocatalytic process similar to prions leading to polymerization. Since then, he has found that platelet-poor plasma (PPP) from patients with acute sequelae of COVID-19 showed extensive fibrin-amyloid microclots that could persist and trap other proteins [160]. Therefore, in addition to neurodegenerative diseases, there are some unknown proteins similar to prions that promote the occurrence of diseases. Further research on the formation, aggregation, and propagation mechanism of these abnormal proteins, and search for ways to inhibit or eliminate these amyloid proteins will provide new ideas for the treatment of diseases.

7. Conclusion

In this article, we systematically review the pathological features and transmission mechanisms of abnormal proteins in prion diseases and other common neurodegenerative disorders, and reveal the central role of protein misfolding and aberrant aggregation in disease pathogenesis. The prion-like behaviours of Aβ, tau, a-syn, and TDP-43 aggregates reveal the potential infectiousness of neurodegenerative disorders, and in particular the medically transmitted nature of the Aβ pathology, providing epidemiological evidence. Although no evidence of person-to-person transmission has been found in diseases other than AD, there is undoubtedly significant risks that need to be focused on preventing medical device-induced healthcare transmission. At the same time, analysing protein misfolding and aggregation mechanisms provide new ideas for the prevention and treatment of neurodegenerative diseases. In order to fully assess the potential risk of transmission of misfolded proteins in humans, it is necessary to implement larger-scale and systematic studies.

CRediT authorship contribution statement

Lan Deng: Writing – original draft, Software, Investigation, Data curation. **Yuanyuan Li:** Writing – original draft, Investigation, Formal analysis. **Ailong Sha:** Writing – review & editing, Supervision, Investigation, Funding acquisition.

Consent to participate

Not applicable.

Availability of data and materials

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

Ethics approval

Not applicable.

Consent for publication

The authors, Ailong Sha, Lan Deng, and Yuanyuan Li have read and approved the fnal manuscript for submission. We confrm the figures are original for this article.

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Declaration of competing interest

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