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Comparative Analysis of Alzheimer‘s Disease and Prion Diseases

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Abstract:

Alzheimer’s disease (AD) is a prevalent neurodegenerative disorder characterized by memory loss, cognitive decline, and personality changes, largely resulting from the misfolding and aggregation of proteins such as amyloid-beta (Aβ) and tau. Similarly, prion diseases (PrD), though relatively rare, are highly lethal and transmissible, involving the misfolding of prion protein (PrP). Both conditions share common pathogenic mechanisms, including the aggregation of misfolded proteins that lead to neurodegeneration. This review compares the pathogenesis of AD and PrD, highlighting the similarities between the proteins involved and their impact on neuronal function. It explores current therapeutic strategies, particularly immunotherapy with monoclonal antibodies, which target pathogenic proteins like Aβ, tau, and PrP. While these treatments show promise in slowing disease progression and alleviating symptoms, challenges such as crossing the blood-brain barrier and managing toxicity remain significant. The findings suggest that insights from PrD may offer new avenues for AD treatment, underscoring the need for further research and clinical trials to develop more effective therapies for neurodegenerative diseases.

Keywords: Alzheimer‘s disease; prion diseases; neurodegeneration.

1. Introduction

Alzheimer’s disease (AD) is a neurodegenerative disease that results from misfolding and aggregation of proteins in the brain. AD is usually characterized by memory loss, personality changes, cognitive impairment, and is sometimes accompanied by a decline in verbal communication skills and executive functions [1]. AD is one of the most common diseases in the world. According to WHO, the global number of people with dementia is expected to increase from 55 million in 2019 to 139 million in 2050 [2]. Meanwhile, AD is currently the seventh greatest cause of mortality worldwide [3]. Therefore, it is crucial to increase the investment in research to treat and prevent AD.

The pathogenesis of AD has been tentatively established. AD is caused by the accumulation of extracellular Aβ plaque and intracellular neurofibrillary tangles (NFT) made of microtubule-associated hyperphosphorylated tau [4]. Additionally, a number of studies have revealed similarities between the pro-

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teins that cause AD (Aβ and tau) and prion disease (PrD). PrD, also known as „transmissible spongiform encephalopathies“, has attracted widespread attention because of their lethality and transmissibility. The most common prion diseases, such as Creutzfeldt-Jakob disease, can deteriorate rapidly and lead to death within weeks or months [5]. The pathogen of prion diseases consists of scrapie prion protein (PrPSc), a misfolded isoform of the normal cellular prion protein (PrP^{C}) [6]. However, unlike the slow aggregation of defective proteins, aggregated PrP^{Sc} induces conformational misfolding of PrP^{C}, allowing prions to proliferate, which is responsible for accelerating disease and death [6].

Given the similarities between the pathogenesis of AD and PrD, there is growing interest in exploring whether therapeutic strategies developed for PrD could be adapted for AD. For instance, treatments aimed at stabilizing protein conformation or preventing the spread of misfolded proteins in PrD may hold promise for AD. Antibody-based therapies had some success with PrP^{Sc} in treating PrD, and their potential to target Aβ and tau in AD is currently being investigated. Although the application of prion diseases to Alzheimer‘s disease is still in its early stages, the underlying mechanistic similarities suggest that these approaches may be valuable in developing more effective therapies for AD.

Currently, treatment strategies for both AD and PrD are limited, with most treatments focusing on reducing clinical symptoms rather than stopping disease progression. In AD, monoclonal antibodies (mAbs) such as donanemab and lecanemab target Aβ aggregates, while in PrD, experimental therapies are exploring ways to inhibit PrP^{Sc} replication. Despite this, there are still significant obstacles. Nevertheless, the prion-like mechanism identified in AD may offer a new therapeutic target, and further research could leverage insights from prion biology to reveal innovative ways to treat or even prevent AD.

2. Pathogenesis of AD

AD is pathologically characterized by synaptic loss, followed by neuronal atrophy throughout the cerebral cortex, with the medial temporal lobe most severely affected [7]. Dense Aβ aggregates and tau neurofibrillary tangles (NTFs) primarily constitute the pathological hallmarks of AD [8]. This is followed by microglial recruitment, which enhances the activation of microglia and local inflammation while also contributing to neurotoxicity [4]. This review will introduce the pathological mechanisms of Aβ and tau respectively.

2.1 APP & Aβ

Aggregated Aβ is a major component of neocortical neuritis plaques and a symbol of brain aging [8]. Aβ, derived from amyloid precursor protein (APP), is a type I transmembrane protein.

APP is involved in a variety of biological processes, including neuronal growth, signalling, intracellular communication, and other functions related to neuronal homeostasis [7]. It is cleaved by β-secretase 1 (BACE1) and γ-secretase to produce insoluble Aβ fibrils. Oligomerization and diffusion of Aβ then result in disrupted synaptic signalling [4]. Insoluble amyloid fibrils aggregate into plaques that spread from the neocortical cortex to the isocortex to the brain stem and eventually to the cerebellum, and Aβ aggregates cause neuronal dysfunction and ultimately neuronal cell death through ion-channel obstruction, altered calcium homeostasis, increased mitochondrial oxidative stress, and reduced energy metabolism and glucose regulation [4].

2.2 NFT & Tau

Another characteristic of AD is the presence of NFTS. These tangles result from hyperphosphorylation of microtubule-associated tau protein [4]. Unlike Aβ, however, normal tau is a naturally folded protein with no intrinsic tendency to aggregate [9]. Tau protein plays a major role in stabilizing microtubules and promoting microtubule assembly [10]. However, when tau interacts with the released kinase, the presence of Aβ in the environment causes hyperphosphorylation of tau [4]. This process was experimentally demonstrated by the fact that Injecting Aβ into transgenic mice‘s brains enhanced tangles while increasing Aβ concentration led to APP overexpression and tau phosphorylation [11]. Tau phosphorylation reduces the stability of tau and microtubules, causing them to lose their tight binding capacity [12]. Tau separates from microtubules, and the dissociated tau proteins self-assemble into oligomers, which then aggregate into NFTs. NFTS are insoluble in neuronal cytoplasm, and aggregation destroys neurons, resulting in aberrant loss of interneuronal connection and signal processing, eventually leading to neuronal apoptosis [4].

The deposition of Aβ and tau in the brain suggests that pathogenic Ab and tau seeds may propagate in their hosts like prions. By comparison, the transmission of Aβ and tau is indeed similar to the pathological mechanism of prions.

3. Pathogenesis of Prion Disease

PrDs are a group of infectious and deadly neurodegen-

erative diseases that can be transmitted within and between species. Mutations in the genes encoding PrP^{C} and PRNP produce PrDs in humans, which results in familial Creutzfeldt-Jakob disease (CJD), Gerstmann-Straussler-Scheinker syndrome, or fatal familial insomnia [6]. These disorders can be inherited or acquired from exposure to prions. Scrapie and bovine spongiform encephalopathy (BSE) are examples of non-human PrDs [6]. Transmission between animals and humans is extremely rare, but humans can also become infected after eating beef from a cow contaminated with bovine spongiform encephalopathy (BSE) [13]. In addition, iatrogenic transmission may occur, such as through organ transplantation or the use of neurosurgical instruments contaminated with prions [13]. The pathogenesis of PrD is characterized by aggregated extracellular deposits of PrP^{Sc} astrocyte formation, and vacuolation, accompanied by neuropathic spongiform changes in the CNS [6].

3.1 PrP Protein

Unlike other misfolded proteins, prions are truly highly infectious and lethal pathogens. In contrast to classical contagious agents, they contain nucleic acids that allow DNA or RNA, the primary structure, to be replicated and amplified (Figure 1). However, PrP^{Sc} reproduction, the culprit that causes prions, does not involve the reproduction of primary structures, but only secondary, tertiary, and quaternary structures, namely their conformations [14]. The reason why PrP^{C} switches to PrP^{Sc} is poorly understood, but it is thought that the α-helix of PrP^{C} switches to the β-rich insoluble conformation (PrP^{Sc}). The β-solenoid in PrP^{Sc} has an intrinsic template function: Its upper and lowest echelons contain „unpaired“ β-chains that can link unfolded PrP molecules by forming hydrogen bonds and induce their conversion into new PrP^{Sc} [15].

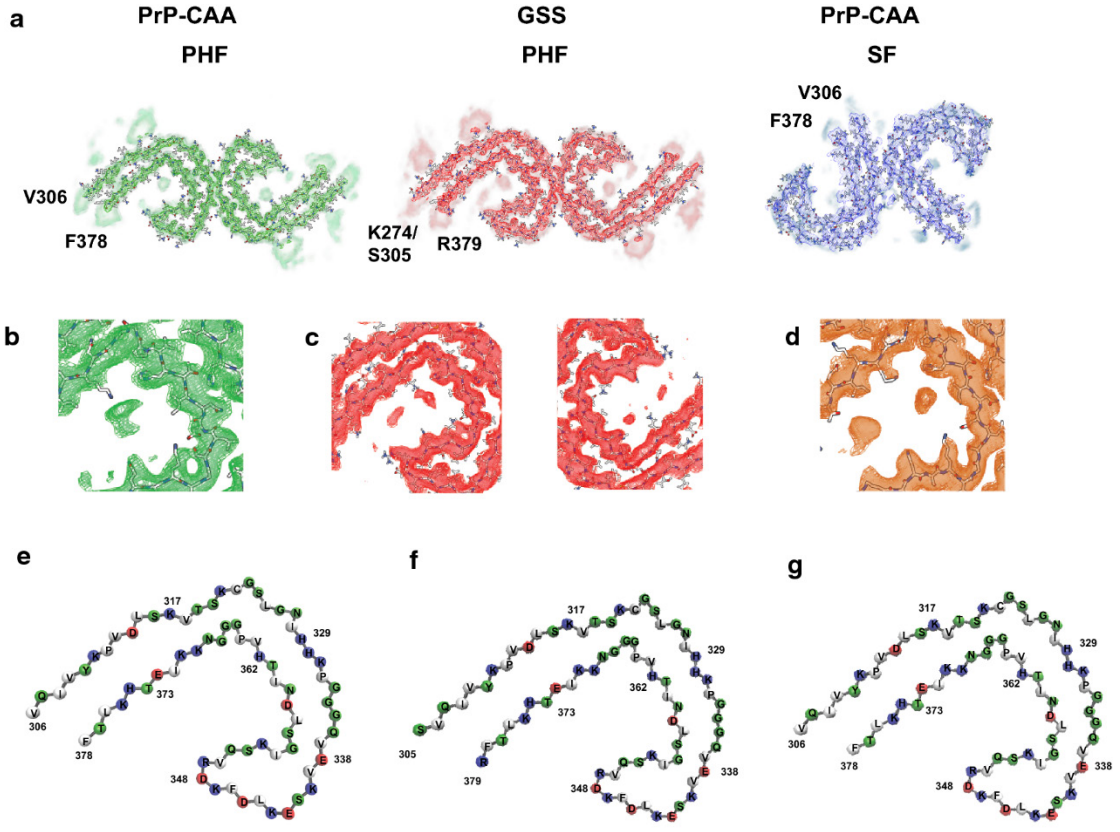

Fig. 1 The structure of Tau filaments in Prion protein amyloidosis [16].

3.2 Spongiform Encephalopathy

The distribution pattern of PrP^{Sc} in the host is complex. It is generally accepted that prions are transported through the blood and lymphatic system into lymphoid tissues for peripheral replication. It is transported to the brain by nerves. Finally, fatal progressive neurodegeneration, spongiosis, and gliosis develop in infected hosts.

3.3 Mainstream Therapeutic Strategies for Brain Degenerative Diseases

Neurodegenerative diseases such as AD and PrD are irreversible, with no complete cure currently. However,

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an analysis of the mainstream treatment approaches for these diseases reveals some similarities. The focus of drug development for PrD is on the transformation process of PrP^{C} and PrP^{Sc} [17]. Similarly, the main therapeutic direction for AD involves targeted therapy for Aβ and tau, which are the pathogenetic proteins of AD. Studies have shown that clinical symptoms of PrD can be alleviated by inhibiting PrP^{C} transport to the cell membrane, stabilizing PrP^{C} structure with chemical chaperones [17], and interfering with PrP^{C} - PrP^{Sc} interaction. This model can also be applied to tau and Aβ due to their similar propagation modes.

3.4 Treatment Methods

Various chemical compounds and antibody-mediated passive immunization have been demonstrated to decrease PrP^{Sc} multiplication and halt the clinical course of PrD [17]. Chemical compounds like pentosan polysulfate (PPS) and Quinacrine can prevent the creation of new PrP^{Sc}. However, these compounds do not significantly affect disease progression or survival rate [17]. Monoclonal antibodies targeting PrP appear to be more effective in some experiments. Mead et al. developed a fully humanized monoclonal antibody against PrP^{C} which proved to be a safe experimental treatment for human prion diseases [18], as it reduces and interrupts the conversion of PrP^{C} to PrP^{Sc}. This treatment also works on Aβ and tau proteins. Monoclonal antibodies (mAbs) targeting Aβ aggregates such as donanemab and lecanemab have been shown to reduce amyloid load as well as slow cognitive decline in patients . There is evidence that these drugs work in patients with tau protein too. Additionally, there is a mAb called ABBV-8E12 which is a humanized mAb against pathological species of tau protein aimed at removing them from brain tissues [18].

4. Discussion

Currently, numerous treatments for PrD and AD are still in clinical trials. While many methods have demonstrated effectiveness on pathological protein structures, they also come with corresponding side effects. In the case of immunotherapy, aside from antibody toxicity, another challenge lies in the blood-brain barrier. Given that many immunoglobulins are large molecules, it is particularly crucial to design antibodies capable of crossing the blood-brain barrier. Targeted therapy is the mainstream direction, although it may not completely cure the diseases, it has shown some efficacy in reducing symptoms and prolonging survival time. Early intervention or using mAbs as a preventive measure may further enhance treatment effectiveness [19]. Furthermore, research has revealed that PrP interaction can effectively inhibit toxic amyloid beta assembly at synapses, offering a new approach to treating AD. Anti-PrP antibodies may potentially play a role in future AD treatment as well [19]. The transmission mechanism of PrD provides new evidence for understanding the pathological mechanism of AD and suggests potential avenues for improving treatment modalities based on this model.

5. Conclusion

AD and PrD are both neurodegenerative diseases and have very high fatality rates. The key difference is that PrD can be transmitted between individuals, while AD is not contagious. However, recent studies have indicated that the pathogenesis of AD is similar to that of PrD. Both of these are caused by the misfolding and aggregation of pathogenic proteins, leading to nerve damage. Analysis of the pathogenesis and current therapeutics for PrD and AD suggests that immunotherapy using monoclonal antibodies targeting the pathogenic protein is more effective and universally applicable. For example, donanemab, a monoclonal antibody against Aβ plague, also appears to be effective against tau. Nevertheless, there remain significant challenges associated with current mainstream treatments, such as the blood-brain barrier and toxicity. Therefore, the development of drugs for neurodegenerative diseases has a long way to go, and clinical trials need to be carefully carried out to find inspiration from similar diseases.

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