A Review of Creutzfeldt-Jakob Disease: Biology, Development, and Current Research

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Abstract

Creutzfeldt-Jakob disease (CJD) is a rare, fatal neurodegenerative disorder caused by prions—abnormally folded proteins. Unlike typical infectious agents, prions lack genetic material and are exceptionally resistant to sterilization. CJD manifests through progressive neurological and psychological symptoms, ultimately resulting in death. It can develop sporadically, genetically, iatrogenically, or through contaminated food. Although no cure currently exists, recent research has shown promising results, including the recent human trial of the monoclonal antibody PRN100. This paper provides an overview of prion biology, the development of CJD, and recent therapeutic research.

What is Creutzfeldt-Jakob disease?

Creutzfeldt-Jakob disease (CJD) is a fatal neurodegenerative disorder caused by proteinaceous infectious particles, also known as prions. Symptoms of CJD typically include difficulty with movement and coordination, vision problems, dizziness, insomnia, social withdrawal, and slurred speech [1]. These neurological and psychological symptoms progressively worsen over time, ultimately leaving affected individuals bed-bound and eventually succumbing to death. Unlike infectious agents such as viruses and bacteria, which contain genetic material, prions are unique in that they do not have genetic material and are highly resistant to heat, radiation, and disinfectants. These characteristics make prions difficult to destroy, presenting major challenges in the development of effective treatments for CJD.

Currently, there is no cure for CJD. Current treatment focuses on alleviating symptoms to ensure patient comfort during CJD's rapid progression. According to the Centers for Disease Control and Prevention (2024), approximately 500–600 cases of CJD are reported annually in the United States. Given its rareness and universal fatality, it is important to deepen our understanding of prion biology to advance the development of effective treatments.

What are Prions?

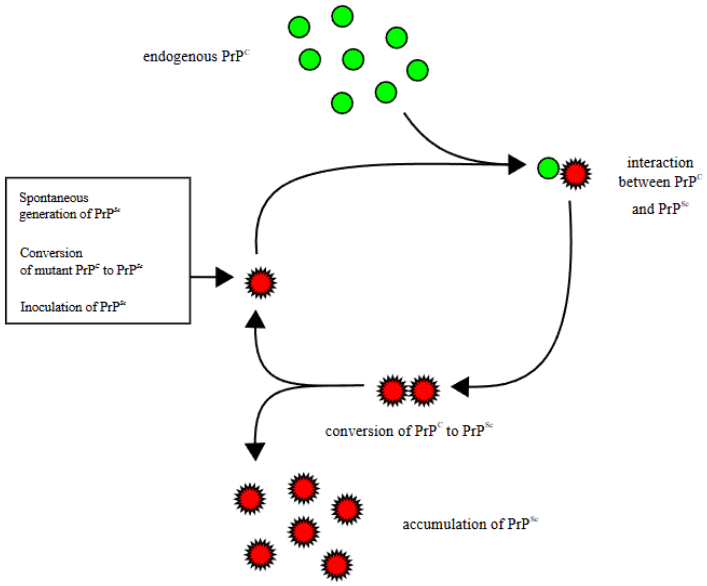
To begin with, prions exist in two main forms: normal and abnormal. The normal form, known as PrPC, is not harmful and its exact biological functions remain unclear. However, they are believed to play a role in cell-to-cell communication and signaling in the brain [2]. Contrastingly, the abnormal form, known as PrPSc, is misfolded and is capable of inducing other normal prion proteins to adopt the same misfolded, infectious structure. Unlike viruses and bacteria, which contain genetic material and reproduce through replication or division, prions are proteins that lack nucleic acids and do not reproduce in a conventional sense. Instead, infectious prions propagate by inducing a conformational change in normal prion proteins, converting them into a contagious form [3].

Prion Propagation

One of the earliest models proposed is the heterodimer model of prion propagation. According to this model, a PrPSc molecule binds to a PrPC molecule, inducing it to misfold. The two then part ways and each misfolded prion is capable of converting additional PrPC molecules [5]. This initiates a chain reaction, resulting in a rapid buildup of PrPSc in the brain. The accumulation of misfolded prions is dangerous because it leads to neural cell death. As brain cells die, they release more PrPSc into the surrounding tissue, spreading the infection further. Over time, the widespread neuronal loss leads to the formation of plaques and causes the brain tissue to develop a sponge-like appearance [2]. The physical deterioration of brain tissue ultimately leads to the neurological and psychological symptoms associated with CJD, including motor dysfunction, cognitive decline, and behavioral changes.

The heterodimer model is just one of several models proposed to explain prion propagation. Other models, such as the nucleation-polymerization model and the template-assisted model, have also been developed to describe aspects of prion behavior. Given the complexity and

unique characteristics of prions, continued investigation into the precise mechanism underlying prion propagation is crucial to the development of effective treatment for CJD. Below is a diagram illustrating the heterodimer model of propagation.



Forms of Creutzfeldt-Jakob Disease

There are four main ways Creutzfeldt-Jakob disease can develop in humans: sporadically, through inheritance, via medical procedures (iatrogenic), and by exposure to contaminated food (variant CJD).

Sporadic CJD is the most common form. As the name suggests, it occurs randomly, without a known cause. In this form, the normal prion protein spontaneously misfolds into the infectious form. The exact trigger for this misfolding is not yet fully understood, but it may involve spontaneous structural changes or genetic mutations that affect the prion protein's stability [2].

Familial CJD, on the other hand, is inherited and results from mutations in the prion-coding gene. It follows an autosomal dominant inheritance pattern. This means that a person only needs to inherit one copy of the faulty gene from either parent to eventually develop the disease. A challenging aspect of familial CJD is that symptoms typically do not appear until later in life. As a result, individuals may unknowingly pass the mutated gene to their children before any symptoms develop [2]. Genetic testing can help identify carriers of the mutation, making early screening and informed family planning important considerations.

Iatrogenic CJD is a form of Creutzfeldt-Jakob disease contracted through certain medical procedures. For instance, between 1958 and 1985, children in the United Kingdom who had growth deficiencies were treated with human growth hormone extracted from the pituitary glands of deceased individuals. Unbeknownst to doctors at the time, some of these hormone preparations were contaminated with infectious prions, leading to the development of CJD in

some patients years later. This is no longer a concern, as the UK began using synthetic growth hormones in 1985, eliminating the risk of prion contamination [2].

Iatrogenic transmission can also occur through neurosurgical procedures. Prions are unusually resistant to standard sterilization methods, so surgical instruments used on a CJD patient may retain infectious material. If these instruments are reused on another patient, the disease can spread. Today, stricter protocols are in place to prevent such incidents [2].

Variant CJD (vCJD), on the other hand, is primarily linked to the consumption of meat products contaminated with bovine spongiform encephalopathy (BSE), commonly known as mad cow disease. To minimize this risk, regulations have been enforced to control what animals are fed, preventing the spread of BSE within livestock and, consequently, reducing its entry into the human food chain [2].

Monoclonal Antibody Therapy in CJD: Evaluating PRN100

In recent years, one significant advancement in the search for a treatment for Creutzfeldt-Jakob disease has been the human trial using a monoclonal antibody called PRN100. This experimental therapy, developed by researchers at University College London, was administered to six patients at the National Hospital for Neurology and Neurosurgery in London. PRN100 is designed to target the normal cellular prion protein (PrPC) in order to prevent its conversion into the misfolded version and halt disease progression. Although the trial demonstrated that PRN100 could be safely delivered to the brain and was well received by patients, it did not prevent disease progression. The main limitations of this study include the small sample size, the absence of a control group, and the late-stage condition of participants. Nonetheless, the trial marks a critical milestone, offering proof for antibody-based therapy in CJD [6].

Conclusion

To conclude, Creutzfeldt-Jakob disease is devastating not only because of its 100% fatality rate but also due to its rapid progression and the elusive, resistant nature of prions. Despite ongoing research efforts, no definitive cure has been developed. Nevertheless, growing insights into prion biology—along with advances in experimental treatments such as PRN100—offer cautious optimism for the future. Only through sustained efforts in both basic and translational science can we hope to transform our understanding of prion diseases into effective, life-saving therapies.

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