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Review

Prion proteins: Physiological functions and role in neurological disorders

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Abstract

Stanley Prusiner was the first to promote the concept of misfolded proteins as a cause for neurological disease. It has since been shown by him and other investigators that the scrapie isoform of prion protein (PrP^{Sc}) functions as an infectious agent in numerous human and non-human disorders of the central nervous system (CNS). Interestingly, other organ systems appear to be less affected, and do not appear to lead to major co-morbidities. The physiological function of the endogenous cellular form of the prion protein (PrP^{C}) is much less clear. It is intriguing that PrP^{c} is expressed on most tissues in mammals, suggesting not only biological functions outside the CNS, but also a role other than the propagation of its misfolded isotype. In this review, we summarize accumulating *in vitro* and *in vivo* evidence regarding the physiological functions of PrP^{C} in the nervous system, as well as in lymphoid organs.
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Contents

1. Introduction

Prion diseases form a group of relatively rare disorders that are both inheritable and transmissible. A common, intriguing feature of all prion disorders is the posttranslational conversion of the endogenous cellular form of the prion protein (PrP^{C}) to the so-called scrapie isoform of prion protein (PrP^{Sc}). The

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PrP^{Sc} isoform is structurally dominated by β-sheet, and relatively resistant to digestion with proteinase K [1,2]. PrP^{Sc} accumulates and can be readily detected in the brain tissue of patients with prion diseases [3,4]. Only in Creutzfeldt–Jakob disease (CJD), the most common human prion disorder, PrP^{Sc} is also abundantly present in secondary lymphoid organs [5–7]. Based on this observation, PrP^{Sc} is considered to be the main component of the transmissible agent [8,9]. The propagation of PrP^{Sc} has been associated with central nervous system (CNS) lesions characterized by astrocyte proliferation, microglial activation, and spongiform vacuolation [3,10]. It has also been suggested that the accumulation of PrP^{Sc} is toxic to neurons [11]. Whether or not there is a direct causal relationship between PrP^{sc} and neuronal cell loss, the exact nature of the cellular insult, and whether PrP^{sc} is the only culprit are some of the issues that remain to be elucidated. For instance, the presence of prion protein peptide 106–126 by itself did not appear to be neurotoxic [12]. Conformational variants of PrP^{Sc} exist, and specific associations with a particular clinical disease phenotype have been described [13]. It is unknown why the deposition of a particular PrP^{Sc} occurs at a particular anatomical location in the CNS in different prion disease [14]. Some data suggest that the conformation of PrP^{Sc} in itself functions as a template in directing the generation of nascent PrP^{Sc}, and explain how diversity prion strains may be encrypted in the conformation of PrP^{Sc} [13].

The group of human prion diseases includes CJD, familial fatal insomnia (FFI), Gerstmann–Sträussler–Scheinker disease (GSS), and Kuru [15,16]. CJD is more common than any of the other disorders: The incidence of sporadic CJD is estimated to be approximately 0.1 new cases per 100,000 per year [17]. Potential difficulties in ascertainment of prion diseases may lead to a significant underestimation of the true incidence and prevalence [17,18]. All prion diseases are invariably fatal.

Cases of CJD have been reported throughout the world. The disease commonly presents with behavioral changes, diffuse myoclonus, and progressive dementia [19]. Disease progression is rapid, and the median life expectancy is currently estimated to be 12 months [19]. Histopathological changes are confined to the cerebral and cerebellar cortices [20]. Intractable insomnia is the clinical hallmark of FFI, a vary rare autosomal dominant inherited prion disorder [21]. Extensive gliosis is present in the medial thalamic nuclei, the anatomical locations that are critical in regulating sleep rhythm [22]. GSS is an autosomal dominantly inherited prion disease that is clinically characterized by ataxia, dysarthria, hyporeflexia, and a mostly progressive dementia [23]. On histopathological examination, amyloid depositions are detectable in the cerebellum [24]. Most suspected cases of human prion diseases are currently diagnosed post-mortem by histopathological and examination of CNS tissue. Diagnostic techniques that would allow the detection of PrP^{Sc} in body fluids would greatly facilitate ante-mortem diagnoses, and may eventually lead to more widely used pharmacological interventions.

Within the group of human prion diseases, a considerable number are caused by mutations in the prion protein gene (*Prnp*) [25]. This is true for CJD, FFI, and GSS. The remainder of cases are the result of PrP^{c} conversion (CJD), exposure to contaminated tissues (CJD), or ritualistic endo-cannibalism (Kuru). Three types of pathogenic *Prnp* mutation have been identified: (A) Point mutations leading to an amino-acid substitution, a (B) premature stop codon, or the (C) insertion of additional octapeptide repeats. Thus far, more than 30 different mutations have been reported in the scientific literature. Human *Prnp* polymorphisms determine the susceptibility to inherited, sporadic, and infectious forms of prion diseases. A polymorphism in the *Prnp* gene that encodes for methionine or valine at codon 129 (*Prnp*129) alters the clinical course and pathological findings of CJD [26–28]. It was also demonstrated that patients who are heterozygous for a *Prnp129* polymorphism that encodes methionine/valine have a later age of disease onset than patient who are homozygous for either amino acid [27]. In FFI, asparagine is replaced by aspartic acid at codon 178 due to a mutation in the *Prnp* gene [29].

In non-human mammals, chronic wasting disease, bovine spongiform encephalopathy (BSE), and scrapie are known prion diseases [15,16,30]. While it had previously been thought that prion diseases were species specific, there is now evidence that species barriers are only relative [30]. New variant CJD is caused by transmission of BSE from cattle to humans [30]. Also, the potential for chronic wasting disease to cross from cervids to humans is considered possible [30]. Ethical and methodological challenges have thus far prevented the screening of individuals at risk for prion disease after possible exposure to infected animal tissue.

While there are currently no proven effective therapies for human prion diseases, monoclonal antibodies have been shown to inhibit prion replication and delay the development of prion disease in the animal models [31]. Furthermore, heterocyclic antiprion compounds have also been undergoing clinical evaluations [32,33].

2. Prions in non-prion diseases of the central nervous system

It was recently shown that *Prnp*129 polymorphisms impact the clinical course of numerous non-prion neurodegenerative disorders of the CNS. *Prnp*129 valine homozygosity appears to increase the risk for early-onset Alzheimer disease [34,35]. The same polymorphism was demonstrated to accelerate the cognitive decline of patients with Down syndrome [36]. The prevalence of the *Prnp*129 heterozygous genotype was also altered in patients with primary progressive aphasia [37]. Recently, our group demonstrated that *Prnp*129 methionine homozygosity results in more severe clinical symptoms in elderly patients with Wilson's disease, particularly with respect to the characteristics of tremor [38]. Other investigators have demonstrated that human *Prnp*129 homozygosity for methionine significantly delays the onset of clinical symptoms in patients with Wilson's disease [39].

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