

The Molecular Pathology of Prion Diseases

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Abstract

Prion diseases, or transmissible spongiform encephalopathies (TSEs), are a group of invariably fatal neurodegenerative disorders. Uniquely, they may present as sporadic, inherited, or infectious forms, all of which involve conversion of the normal cellular prion protein (PrP^C) into a pathogenic likeness of itself (PrP^{Sc}). Formation of neurotoxic PrP^{Sc} and/or loss of the normal function of native PrP^C result in activation of cellular pathways ultimately leading to neuronal death. Prion diseases can affect both humans and animals, with scrapie of sheep, bovine spongiform encephalopathy (BSE), and Creutzfeldt-Jakob disease being the most notable. This review is intended to provide an overview of the salient scientific discoveries in prion research, mainly from a molecular perspective. Further, some of the major outstanding questions in prion science are highlighted. Prion research is having a profound impact on modern medicine, and strategies for prevention and treatment of these disorders may also find application in the more common neurodegenerative diseases.

Keywords

Prion protein, transmissible spongiform encephalopathies, Creutzfeldt-Jakob disease, protein aggregation

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Introduction

The idea of disease-causing protein particles was first put forward in 1982 by Stanley B. Prusiner, the neurologist who coined the term 'prion' (from proteinaceous infectious particle). He was subsequently awarded the 1997 Nobel Prize in Physiology and Medicine for this discovery, a discovery that heralded the start of a new chapter in medical textbooks. Prion diseases, or transmissible spongiform encephalopathies (TSEs), are a group of fatal neurodegenerative disorders that affect both humans and animals.¹ Human prion diseases are unique in that they can have a sporadic, inherited, or transmissible aetiology.² The hallmark event in all TSEs appears to be the misfolding of the normal cellular prion protein (PrP^C), which is found predominantly on the outer surface of neurons, into an insoluble protease-resistant conformation (PrP^{Sc}). The abnormal PrP^{Sc} isomer is then believed to catalyse the conversion of normal PrP^C into a likeness of itself. In sporadic prion disease, this change in protein structure occurs spontaneously, as a chance event, or possibly because of a somatic mutation in the prion gene which destabilises PrP^C and increases the likelihood for the conformational conversion to occur. In the familial prion diseases, it is the inherited genetic mutation that directly predisposes to this conversion. In the transmissible scenario, the interaction of host PrP^C with exogenously introduced PrP^{Sc} initiates the autocatalytic process. In all three situations, the end result is loss of function of the native PrP^C coupled with a toxic gain-of-function of aggregated PrP^{Sc}. To date, various experiments support the idea that the sole agent required for transmission of prion disease is simply the abnormal prion protein isoform.³ For instance, it has been found that familial forms of human prion disease can be transmitted to laboratory animals by inoculation. Naturally, PrP^{Sc} requires endogenous host PrP^C to propagate: knock-out transgenic mice that lack prion protein expression (*Prnp^{0/0}*) are completely resistant to PrP^{Sc} infection.⁴ Indeed, this form of pathogenesis is unique among human disease, and a revolutionary idea in clinical medicine.

BSE and variant CJD

Most cases of human prion disease are sporadic; sporadic Creutzfeldt-Jakob disease (CJD) occurs in a random distribution all over the world and has an annual incidence of one per million. The inherited group make up approximately 15% of human prion disease, and all cases to date have been associated with

coding mutations in the prion protein gene. The use of genetic diagnosis has in fact resulted in the inclusion of some atypical dementias and fatal familial insomnia as part of the spectrum of human prion disease.² It is transmissible CJD which, however, has attracted the lion's share of public and media attention; the first case of variant CJD (vCJD) was described in 1995 in the UK, and since then speculation has been rife about a possible epidemic.⁵ The story most likely began when the infectious agent that causes scrapie in sheep crossed the species barrier to bovines to cause bovine spongiform encephalopathy (BSE). This happened in the UK and not elsewhere because of the relatively high incidence of scrapie in the UK, as well as the elimination of a step in the processing of livestock carcasses that allowed the infectious prion to survive.⁶ Then, once the species barrier from sheep to cattle had been crossed, recycling of the bovine-adapted scrapie amplified the infection and resulted in a BSE epidemic. That BSE originated from contaminated meat and bone meal has been vindicated by the fact that the 1988 ban on such products effectively halted the spread of BSE.⁷ Meanwhile, however, the infectious prion agent had progressed further: it had also managed to pass on from bovines to humans, giving rise to vCJD (i.e. human-adapted BSE). To date, over 130 victims have been claimed by vCJD, ascribed to consumption of BSE-contaminated foodstuffs as the most likely explanation. That BSE and vCJD are caused by the same prion strain is now a well-confirmed scientific fact.² To start with, molecular strain typing studies have shown that all cases of vCJD are associated with the type of PrP^{Sc} that is also observed in BSE, whilst differing from the PrP^{Sc} types found in sporadic CJD. Moreover, it has been demonstrated that human vCJD prions precisely duplicate the properties of native bovine BSE prions in their behaviour on transmission to experimental mice.⁸ This is a very strong argument for an aetiological link between BSE and vCJD. Finally, it must be mentioned that BSE-like prion strains have been identified as the cause of novel spongiform encephalopathies in various animal species, such as domestic and captive wild cats (feline spongiform encephalopathy) including cheetahs, pumas and tiger, and in exotic ungulates such as the bison, Arabian oryx, and others. This transmission of BSE prion to other species constitutes an additional potential risk to human health.

Prion transmission in variant CJD

Transmission of infectious prions does not occur by direct contact, but *via* the peroral or parenteral routes.⁹ In an oral uptake scenario, prions have to make their way from the gastrointestinal tract to the central nervous system (CNS). Interestingly, both intestinal epithelial cells and lymphoid cells are known to express PrP^C, thereby making ideal vehicles for prion transmission. It is thought that following oral uptake, prions first gain entry into the intestinal mucosa, perhaps through antigen-presenting M cells, and then proceed to reach various gut-associated lymphoid tissue (GALT) components and submucosal/myenteric enteric nervous system ganglia.

Thereafter, prion infection spreads from the gut to the brain along the peripheral nervous system, either directly via the vagus nerve, or via the spinal cord through the sympathetic nervous system.¹⁰ Pathological PrP can be detected in tonsils, lymph nodes, spleen, and appendix, even in the preclinical stages of the disease.¹¹ As regards the role of blood in transmission, suffice it to say that using the macaque model it has been shown that BSE can be transmitted from primate to primate in 25 months by the intravenous administration of infected brain homogenate solution.¹² Also, the BSE agent adapts to macaques in the same way as it does to humans: examination of macaque brain inoculated with vCJD (macaque vCJD) revealed a similar pathology to that with second-passage BSE (macaque-adapted BSE).¹² Indeed, human-adapted BSE is more virulent for humans than cattle BSE and is efficiently transmitted by the peripheral route.¹² Clearly, therefore, the risk of iatrogenic transmission of vCJD through surgical instruments, grafts, or blood transfusion is real but at the same time difficult to assess. In a recent study on the experimental transmission of surface-bound infectious prions it was reported that five minutes of contact with brains of scrapie-infected mice sufficed for a stainless steel wire to acquire a maximum load of infectivity.⁹

Documented cases of iatrogenic CJD include those resulting from transmission via neurosurgical instruments, human dura mater grafts, corneal transplants, and treatment with human pituitary hormones (growth hormone and gonadotrophin).¹³ All these transmissions involved parenteral inoculation either by surgical or by intramuscular injection. Mean incubation periods varied from 1-2 years in neurosurgical transmission (in view of direct cross-contamination with material in or adjacent to the brain), to 10-15 years in human pituitary hormone treatment. There is uncertainty as to the risk of transmission of CJD by blood products, particularly since the presence of CJD infectivity in human blood is still not clearly established. In contrast, blood infectivity in rodent models of CJD has been well described and is detected in the incubation period, well before onset of neurological signs.¹⁴ Quite recently, the national CJD surveillance unit in the United Kingdom reported a case of vCJD who had received a blood transfusion from a donor who later died of vCJD¹⁵; moreover, a case of preclinical vCJD was also identified in a patient who died from a non-neurological disorder just 5 years after receiving blood transfusion from a donor who later developed vCJD.¹⁶ These findings certainly raise the likelihood of transmission of vCJD by blood transfusion.

Guidelines have been drawn up in some countries to minimize the risk of iatrogenic transmission of CJD and modern sterilization techniques, for example porous autoclaving at 134°C for 18 minutes, have been demonstrated to significantly reduce infectivity. Human growth hormone was withdrawn in many countries in 1985 and has been replaced by recombinant therapy. Dura mater grafts are no longer used in many countries. In the UK, leuco-depletion of all blood donations has been introduced, while individuals at greater risk of developing CJD have been excluded as blood donors in many countries. These

measures significantly reduce the possibility of iatrogenic transmission of CJD, but do not exclude it.

The “species barrier”

The likelihood of transmission of prion disease from one mammalian species to another is limited by the so-called ‘species-barrier’. In other words, same-species transmission of prions is typically highly efficient, whilst there is a relative lack of susceptibility of one species to prions derived from another species. The biological consequence of a species barrier is thus an increase in mean incubation time and a reduction in the fraction of animals succumbing to disease. The molecular basis of the species barrier is believed to reside in differences between the primary amino acid sequence of the host and inoculum prion proteins. To cite an example, transgenic mice expressing hamster PrP^C are much more susceptible than wild-type mice to infection with hamster PrP^{Sc}.¹⁷ However, the ‘species difference’ is not the only determinant. For instance, classical CJD prions and vCJD prions do not transmit equally to wild-type mice, even though both prion strains have the identical primary structure of human PrP^C: in fact, vCJD prions transmit much more readily than do CJD prions from sporadic disease.¹⁹ Evidently, factors like tertiary and quaternary protein structures also influence prion propagation. Overlap between a thermodynamically favoured PrP^{Sc} conformation and that of the host PrP^C might therefore result in relatively easy transmission between two species. In this respect, BSE prions might represent a particularly stable PrP^{Sc} conformation that is also favoured by PrP^C from a wide range of different species, thereby accounting for the remarkable promiscuity of this strain in mammals. Regarding species barriers, recent data has emerged that has proved quite unsettling. In particular, conventional mice were considered to have a high barrier to hamster PrP^{Sc} inoculation since no clinical signs of scrapie develop in such mice within their normal lifespan. Nevertheless, careful study revealed the presence of high PrP^{Sc} titers in their brains. Moreover, infectivity was successfully passaged from the scrapie-inoculated asymptomatic wild-type mice to both other mice and hamsters. In effect, this was a demonstration of subclinical prion infection, where animals can harbour high levels of infectivity without developing clinical signs of prion disease.²⁰ Such results seriously put to question our current definition of the species barriers, which has classically been based on clinical end-points.

Clinical features and diagnosis of classical and variant CJD

Sporadic CJD usually affects individuals between the ages of 45 and 75 years, and presents as a rapidly progressive dementia. Typically, onset is subtle and followed by a very rapid deterioration, with a total duration of less than 6 months. Prodromal complaints include relatively non-specific symptoms like fatigue, malaise, insomnia, dizziness, and memory difficulties. Later, neurological symptoms and signs develop

rapidly: difficulty with gross and fine motor movements, myoclonus, cerebellar ataxia, aphasia, eating and/or swallowing difficulties. In variant CJD, the person affected is typically under 50 years of age, often under 30, and initially psychiatric symptoms predominate, together with non-specific fatigue and sleep disturbance. The most prominent psychiatric manifestation is depression; however, apathy, withdrawal, anxiety, aggression, delusions, and auditory and visual hallucinations are also encountered. With disease progression, neurological problems arise: painful sensory symptoms, ataxia, chorea, rigidity, aphasia, blurred vision and diplopia. In contrast to sporadic CJD, dementia usually develops later in the clinical course of vCJD.

Until recently, the clinical diagnosis of CJD relied mainly on a detailed case history and typical EEG findings.²¹ The latter consist of characteristic periodic and pseudoperiodic sharp or triphasic wave complexes of 0.5 to 2.0 Hz against a slow background. A negative EEG does not exclude the diagnosis of CJD, particularly in the variant form. Criteria have been extended to include CSF analysis (e.g. 14-3-3 protein) for sporadic CJD and MRI scans in vCJD.²² The level of 14-3-3 protein increases in neuronal death, and is therefore not specific for CJD. However, levels of the gamma-isoform of 14-3-3 in CSF samples from CJD patients were found to be significantly higher than those observed in patients with non-CJD demetias.¹⁸ Typical MRI changes include increased signal in the basal ganglia in sporadic CJD, contrasting with a posterior thalamic high signal in vCJD.²³ Additionally, vCJD can be diagnosed by detection of vCJD-specific PrP^{Sc} on Western blot of a tonsil biopsy; there is no comparable involvement of tonsil and other lymphoreticular tissues in classical CJD.²⁴ Brain biopsy has also been used to diagnose CJD in life and may have a high diagnostic accuracy. However, a negative biopsy result does not exclude the diagnosis of CJD because of the possibility of sampling error, and the procedure does have risks to the patient. A firm diagnosis of CJD, therefore, often depends on neuropathological examination post-mortem. In common with other TSEs, neuropathological characteristics include neuronal cell loss, spongiform degeneration, and gliosis with hyperastrocytosis; the neuropathological hallmark of vCJD is the presence of numerous florid amyloid plaques throughout the cerebral and cerebellar cortices.²⁵ There is hence an urgent need for the development of sensitive assays based on blood or urine for ante mortem diagnosis of BSE/vCJD. A problem here is that the concentration of PrP^{Sc} in the blood is much lower than in the CNS; in particular, in human prion disease PrP^{Sc} has not been demonstrated in the blood. Thus, novel immunoassays and immunoquantitative PCR assays are being developed for ultrasensitive detection of the TSE agent. Also, an antibody has been generated which specifically recognizes PrP^{Sc} and can discriminate between the different PrP^{Sc} conformers from sporadic and vCJD. Preliminary data suggests that a reduced expression of prion protein in the whole blood of patients with vCJD may be useful as a surrogate marker for vCJD.

Regarding host susceptibility to the development of CJD, the role of the polymorphism in the prion protein gene at codon 129 should be mentioned. At PrP codon 129, an amino acid polymorphism for methionine valine has been identified. In the general Caucasian population, the frequencies for the codon-129 polymorphism are 12% Val/Val, 37% Met/Met, and 51% Met/Val.² This contrasts with sporadic CJD patients, most of whom are homozygous for methionine or valine, or variant CJD cases all of whom to date have had a methionine homozygosity.² Very recently, however, preclinical CJD was found in a PrP codon 129 heterozygous individual, suggesting that susceptibility to vCJD infection may not be confined to the methionine homozygous genotype.¹⁶

Mechanisms of spongiform neurodegeneration

Another unanswered question in prion science pertains to the pathogenic cascades that result in neuronal loss.^{3,26} PrP conversion might promote disease either by loss of function of the natively folded PrP^C or by gain of toxic activity of PrP^{Sc}. Concerning the latter, neurografting experiments have revealed that despite formation of substantial amounts of PrP^{Sc} in the brain, *Prnp*^{0/0} neurons remain unaffected.²⁷ A possible explanation of these results is that PrP^{Sc} deposited extracellularly is not, in itself, damaging to neurons and that prion-induced neurodegeneration is instead the consequence of *de novo* PrP^{Sc} formation at the cell surface or within cells. The question of whether loss of function of PrP^C contributes to pathogenesis cannot be ascertained until the normal physiology of PrP^C in the brain is unravelled.²⁸ The prion protein is highly conserved in mammalian species³⁹ and although expressed most abundantly in the brain, it has also been detected in other non-neuronal tissues as diverse as lymphoid cells, lung, heart, kidney, gastrointestinal tract, muscle and mammary glands.²⁹ Such properties point to a basic biological role of the molecule. The most salient observations of prion physiology can be summarized as: (i) a role in copper homeostasis, particularly at the pre-synaptic membrane;^{30,31} (ii) involvement in signal transduction cascades and calcium homeostasis;³¹⁻³⁶ and (iii) involvement in cellular survival against copper and oxidative stress.³⁷⁻³⁸ Over the past years, evidence has been accumulating that oxidative stress plays a central role in pathogenesis of TSEs.⁴⁰ To start with, lack of PrP^C results in neuronal phenotypes sensitive to oxidative stress. Secondly, there is abundant evidence of oxidative stress in cellular and animal models of prion disease. Thirdly, markedly increased levels of lipid and protein oxidation were found in brain lysates from sporadic CJD subjects. In view of the above, anti-oxidant therapeutic strategies are believed to have real potential in the treatment of TSEs.

Conclusion

The future of prion research promises to be very challenging and exciting. Twenty or more human diseases are associated with the deposition of β -sheet-rich protein aggregates, or amyloid.⁴¹ These include some neurodegenerative diseases, such as Alzheimer's, Parkinson's, polyglutamine expansion, amyotrophic lateral sclerosis, and prion diseases. Hence, prion research is also contributing to our knowledge of how pathogenic aggregation-prone proteins compromise neuronal plasticity and survival.⁴² Research at a more fundamental level could identify a prominent role for prion-like mechanisms, in which a protein achieves a self-perpetuating state, in several different biological contexts. This novel concept in biology has already been found to operate in long-term memory storage.⁴³ Last, but not least, it is necessary to sustain worldwide CJD surveillance regardless of national BSE incidence and to take all precautionary measures to avoid iatrogenic transmissions of vCJD.

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Corinthia Group Prize in Paediatrics, 2004

Dr Jacques Diacono was this year's successful prize winner in Paediatrics, having obtained the top aggregate mark over the combined examinations in Paediatrics in the fourth and final year of the undergraduate course. Dr Diacono also placed first overall in Medicine in this year's final examination. Competition for the now well-established Corinthia Group Prize in Paediatrics was as stiff as ever, with several candidates vying for the honour! Indeed, we would sincerely like to congratulate all those undergraduates (now doctors) who performed admirably during the undergraduate course in Paediatrics. We would also like to offer our congratulations to Dr Diacono, seen receiving a cheque for Lm100 from Dr Simon Attard Montalto, Head Department of Paediatrics. Finally, we are extremely grateful to the Corinthia Group for their ongoing support toward the Academic Department of Paediatrics.

