Is loss of function of the prion protein the cause of prion disorders?

Claudio Hetz, Kinsey Maundrell and Claudio Soto

Serono Pharmaceutical Research Institute, 14 Chemin des Aulx, 1228 Plan les Ouates, Switzerland

Transmissible spongiform encephalopathies are fatal neurodegenerative diseases that involve misfolding of the prion protein. Recent studies have provided evidence that normal prion protein might have a physiological function in neuroprotective signaling, suggesting that loss of prion protein activity might contribute to the pathogenesis of prion disease. However, studies using knockout animals do not support the loss-of-function hypothesis and argue that prion neurodegeneration might be associated with a gain of a toxic activity by the misfolded prion protein. Thus, the mechanism of neurodegeneration in spongiform encephalopathies remains enigmatic.

Transmissible spongiform encephalopathies (TSEs), also known as prion disorders, are a group of rare fatal neurodegenerative diseases affecting humans and other animals. The group includes several clinically diverse but mechanistically similar neurological diseases, such as Creutzfeldt–Jakob disease (CJD), fatal insomnia, Gerstmann–Straussler syndrome (GSS) and kuru in humans, as well as bovine spongiform encephalopathy (BSE), scrapie and chronic wasting disease in animals. The hallmark event in all TSEs appears to be the misfolding of the prion protein (PrP), leading to the accumulation of protease-resistant insoluble deposits in the brain [1]. A large body of evidence supports the conclusion that PrP misfolding is the cause of TSEs (for a review, see [2]). Human PrP is the product of a single gene, *Prnp*, which directs the synthesis of a protein containing 253 amino acid residues, with five octapeptide repeats near the N-terminus, two glycosylation sites and one disulfide bridge. In addition, a glycosylphosphatidylinositol anchor (GPI) attaches the protein to the outer surface of the cell membrane. The *Prnp* gene is constitutively expressed in the brain and other tissues of healthy individuals and there are three glycoforms of the protein: mono-, di- and un-glycosylated. However, no sequence or post-translational differences have been detected between the normal host-cell-surface PrP, termed PrP^{C}, and the pathological isoform, PrP^{Sc} [3]. The conversion of PrP^{C} into PrP^{Sc} involves a conformational change, in which the α-helical content decreases and the β-sheet content increases [4].

In most cases of TSE there are no recognizable gross abnormalities in the brain. However, patients who survive for several years show variable degrees of cerebral atrophy, comparable to those observed in other neurodegenerative diseases. The typical microscopic features of TSEs are vacuolation of the neuropil in the grey matter, prominent neuronal loss, exuberant reactive astrogliosis and a variable degree of cerebral accumulation of PrP aggregates [5–7]. The spongiform degeneration consists of diffuse or focally clustered, small, round vacuoles that can become confluent [7], although the contribution of the vacuolization process to the pathogenesis of the disease is not yet clear [8]. Neuronal loss occurs by apoptosis (programmed cell death) and is the most likely cause of brain malfunction [9]. Brain inflammation is prominent in TSEs, but it is rather unusual in that it largely involves activation of brain cells (astrocytes and microglia) [10]. All of the known prion diseases in animals and humans lead to the accumulation of abnormal prion protein aggregates in the central nervous system, sometimes in the form of amyloid plaques similar to the lesions found in other neurodegenerative illnesses, such as Alzheimer's disease [11,12].

Although neuronal loss is probably the direct cause of the clinical symptoms of TSEs, their origin and mechanism, particularly in relation to the prion replication process, are still poorly understood. PrP conversion might promote disease either by loss of function of the natively folded PrP^{C} or by gain of a toxic activity of PrP^{Sc}. Over many years, much research has been devoted to the nature of the infectious agent itself and to the mechanism of prion replication and, recently, several reports have started to provide insight into the potential biological function of normal PrP^{C}. In this article, we assess the latter research with the aim of evaluating the normal role of PrP^{C} in relation to neurodegeneration.

Neuroprotective signaling through prion protein?

The prion protein is constitutively expressed on neurons, and is evolutionarily conserved. It is mainly localized at synapses, in cholesterol-rich microdomains of the plasma membrane known as caveolae [3,13]. The high concentration of receptors and other signaling molecules in these structures provided the first hint of a potential signaling role of PrP^{C}. Support for this idea came from antibody-mediated cross-linking experiments, which showed a caveolin-1-dependent coupling of PrP^{C} to Fyn, a member of the Src family of tyrosine kinases [14]. Although these results suggest that PrP^{C} might function as a signaling molecule, the authors were unable to detect any of the

Corresponding author: Claudio Soto (claudio.soto@serono.com).

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expected morphological responses downstream of Fyn. In addition, there is no reported evidence that activation of Fyn is a physiological pathway operating *in vivo*. Other signaling proteins have also been proposed to bind PrP^C. For example, using a yeast two-hybrid approach, neuronal phosphoprotein synapsin Ib, the adaptor protein Grb2, and the still uncharacterized prion interactor protein Pint1 were identified as potential interacting proteins [15]. The *in vivo* interaction of these proteins with PrP^C was supported by co-immunoprecipitation, but no indication of the physiological relevance of these interactions is yet available.

Evidence supporting the hypothesis that PrP^C plays a role in neuroprotective signaling has come from recent studies by Vilma Martins and co-workers. Using complementary hydropathy analysis, they identified stress-inducible protein 1 (STI1) as a potential PrP^C-interacting protein in the plasma membrane [16]. STI1 is a heat-shock protein, first described in a complex with the heat-shock protein 70 (Hsp70) and Hsp90 chaperone family of proteins [17,18]. Using organotypical retinal explants, the interaction between PrP^C and STI1 was shown to protect neurons from anisomycin-induced apoptosis [16]. This phenomenon was not observed in tissues derived from *Prnp*-null mice. A detailed analysis of the signaling pathways involved in PrP^C-mediated neuroprotection was performed using a peptide ligand identified by complementary hydropathy [19]. The interaction of PrP^C with this peptide induced activation of the cAMP-dependent protein kinase A (PKA) and extracellular-signal-regulated kinase (ERK) pathways. Activation of the PKA pathway has been shown to be involved in the inhibition of anisomycin-induced apoptosis, whereas activation of the ERK pathway promotes apoptosis. These findings suggest that the balance between pro- and anti-apoptotic signals might determine the physiological consequence of PrP^C engagement. Interestingly, the peptide ligand used to activate PrP^C signaling was shown to interact with the PrP fragment 113–128, which overlaps the neurotoxic PrP106–126 region [19]. Synthetic peptides corresponding to the PrP sequence 106–126 mimic the physicochemical features of PrP^{Sc}, and have been used extensively to study the putative PrP^{Sc} neurotoxicity *in vitro* and *in vivo* [20–22]. PrP106–126 completely inhibits binding between the peptide ligand and PrP^C, and abolishes the neuroprotective effect triggered by this interaction. Based on these findings, it is possible to propose a model in which PrP^C interacts with an endogenous ligand (possibly STI1) and constitutively transduces a survival signal through the PKA pathway (Fig. 1).

This model provides an alternative explanation for the mechanism of PrP106–126 neurotoxicity, in which PrP106–126 is not toxic *per se* (a widely held view) but rather suppresses a neurotropic signal by competing for the interaction between PrP^C and its endogenous ligand. This interpretation also provides an explanation for the observation that *Prnp* expression is required for PrP106–126 toxicity [23]. In addition, it is possible to speculate that during the development of prion diseases, the conformational changes associated with PrP conversion result in decreased affinity for the ligand, thus eliminating the PrP^C-mediated neuroprotective effect. Additional support for a neuroprotective role of PrP^C comes from studies with neuronal primary cultures, showing that $Prnp^{-/-}$ cells are more sensitive than wild-type cells to apoptotic stimuli, such as serum deprivation [24].

Despite the evidence for a neuroprotective role of PrP^C, it remains unclear how a GPI-anchored protein can initiate a signaling cascade, because activation of adenylate cyclase is dependent on the activity of proteins, such as G proteins, located on the inner side of the plasma membrane. In this context, it is interesting that GPI-anchored proteins (including PrP^C) and G-protein-coupled receptors, are located together in caveolae-like domains. However, there is currently no evidence of an increase in

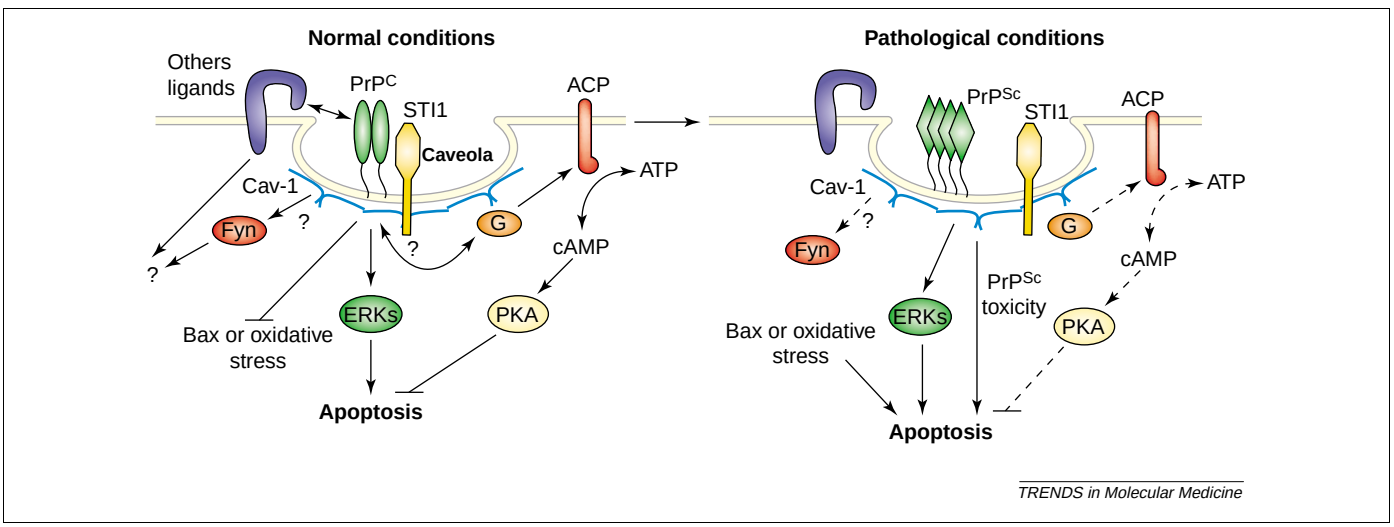

Fig. 1. Signal transduction through the prion protein (PrP). Under normal conditions, the interaction between normal PrP (PrP^C) and its ligand [stress-inducible protein 1 (STI1) or others] might potentially lead to alterations in several signaling pathways: (1) activation of a putative G protein (G), which in turn activates an adenylate cyclase (ACP), leading to the formation of cAMP and activation of protein kinase A (PKA); (2) activation of the extracellular-signal-regulated kinases (ERKs) pathway, promoting neuronal death; (3) inhibition of the mitochondrial apoptotic pathway through a Bcl-2-like activity; and (4) Caveolin-1 (Cav-1)-dependent activation of the tyrosine kinase Fyn, with unknown consequences. During prion disease development, the conformational changes associated with production of the pathological form of PrP (PrP^{Sc}) might lead to a reduction of the neuroprotective signals and/or an exacerbation of neurotoxic signaling.

cAMP following cross-linking of GPI-anchored proteins. Hence, the precise mechanism of PrP^C-mediated signaling remains speculative, and more research is required to clarify this key issue.

Other putative physiological functions of PrP^C

Searching for PrP-interacting proteins has been a general approach in attempting to understand the function of PrP^C. In addition to the proteins described above, other candidate ligands for PrP^C include Bcl-2, Hsp60, Bax-inhibiting peptide, nuclear respiratory factor 2, apolipoprotein A1, neural cell-adhesion molecules, heparin, laminin and laminin receptor (reviewed in [25]).

PrP fusion proteins interact with Bcl-2, as shown by yeast two-hybrid experiments and by co-immunoprecipitation [26]. A functional relationship between PrP^C and the Bcl-2 anti-apoptotic proteins is suggested by experiments showing that overexpression of the gene encoding Bcl-2 can attenuate the increased susceptibility to serum-deprivation-induced apoptosis of *Prnp*-null neurons *in vitro* [24]. A link between PrP and the Bcl-2 family is also suggested by the similarity between the highly conserved octapeptide repeats of PrP and the Bcl-2 homology domain 2 (BH2) common to the Bcl-2 protein family. The BH2 domain is crucial for the anti-apoptotic function of Bcl-2 and its interaction with the pro-apoptotic protein Bax, suggesting that PrP might be a member of the anti-apoptotic family. Support for this hypothesis comes from *in vitro* experiments showing that PrP^C can protect human neurons against Bax-induced apoptosis [27]. This neuroprotective activity was not observed with mutant PrP bearing deletions of the octapeptide repeats or carrying C-terminal mutations associated with inherited prion diseases [27]. These results are consistent with observations from transgenic mice expressing mutant PrP devoid of the octapeptide repeats, which show alterations in incubation time and histopathology during infection with scrapie [28]. The major problem with the hypothesis of PrP^C being an anti-apoptotic protein like Bcl2 is that it has not been shown to be present in cytoplasm, mitochondria or the outer surface of endoplasmic reticulum, where the Bcl-2 family normally exerts its activity.

Another widely studied putative function of PrP^C is in the binding and metabolism of copper [29]. The link between copper and TSEs comes from studies carried out 30 years ago, showing a prion-like spongiform degeneration of the brain following treatment of animals with the copper chelator, cuprizone [30,31]. The octapeptide repeats of PrP^C are able to bind copper within the physiological concentration range [32,33], suggesting that PrP^C might have a role in normal brain copper metabolism. Overexpression of *Prnp* has been shown to increase copper uptake into cells and to enhance copper incorporation into superoxide dismutase. Furthermore, the prion protein itself has a weak superoxide dismutase activity *in vitro* [34], which is dependent on copper binding to the octapeptide repeats. Interaction between PrP^C and either PrP^{Sc} or PrP106–126 inhibits the superoxide dismutase activity, suggesting that PrP misfolding, with a concomitant loss of enzyme function, could contribute to neuronal damage [29]. *In vivo* experiments have shown that *Prnp*-null mice have lower brain copper levels and elevated copper in serum compared with wild-type mice [33]. However, another study found no differences in the copper levels in brain of transgenic animals expressing different quantities of PrP^C [35].

There is a significant change in the levels of copper in the brains of scrapie-infected mice, before the onset of clinical symptoms [36,37]. Analysis of purified PrP from the brains of these mice also showed a reduction in copper binding to the protein and a proportional decrease in anti-oxidant activity, between 30 and 60 days post-inoculation [36]. In addition, it has been reported that in human sporadic CJD there is a decrease of up to 50% in brain copper levels [38]. Hence, PrP^C could be an important brain membrane copper-binding protein that participates in copper homeostasis, and PrP misfolding might result in abnormal brain metal levels, leading to neuronal damage [29]. PrP^C is constantly endocytosed, passing through an early endocytic compartment before being restored to the plasma membrane [13,39]. Copper ions have been reported to stimulate rapidly and reversibly the internalization of PrP^C [40]. It has been proposed that copper binding increases the affinity of PrP^C for an endocytic receptor, leading to internalization of PrP^C and copper, and hence PrP^C could serve as a recycling receptor for uptake of copper ions from the extracellular milieu. The interaction of copper with PrP might also modulate conversion of the normal protein into the pathological isoform. Indeed, it has been shown that the binding of Cu^{2+} causes a change in both the tertiary and secondary structure of PrP, leading to the formation of a protease-resistant form [41]. Copper binding increases the stability of the β-sheet and thermodynamically promotes the shift from α-helical to the β-sheet associated with PrP^{Sc}.

It remains to be demonstrated whether anti-apoptotic activity or copper binding are indeed biological functions of PrP^C and what their contribution is to TSE pathogenesis. Nevertheless, PrP^C appears to be a multifunctional protein (Fig. 2), in which different structural domains participate in diverse activities, including binding to different ligands, initiation of signal transduction events, regulation of synaptic functions, copper binding and anti-oxidative activities.

Another issue that has yet to be resolved is the subcellular localization of PrP most relevant to TSE pathogenesis. Until recently, it was thought that membrane GPI-anchored PrP either exposed on the cell surface or in the endocytic pathway was most important to PrP^C biological function, as well as being the site of conversion. However, recent evidence has suggested that cytosolic or transmembrane PrP molecules exist and might play a role in disease pathogenesis. In some inherited cases of prion diseases, it has been reported that the predominant form of PrP detectable in the brain is not PrP^{Sc}, but rather a transmembrane form of the prion protein, named ^{CTM}PrP [42,43]. This is associated with a subset of patients with GSS, carrying the mutation A117V. Interestingly, this mutant protein leads to degeneration in transgenic mice, in the absence of PrP^{Sc} generation and infectivity, when inoculated in the brain of rodents. The role of ^{CTM}PrP in TSE pathogenesis is still unclear, and future research

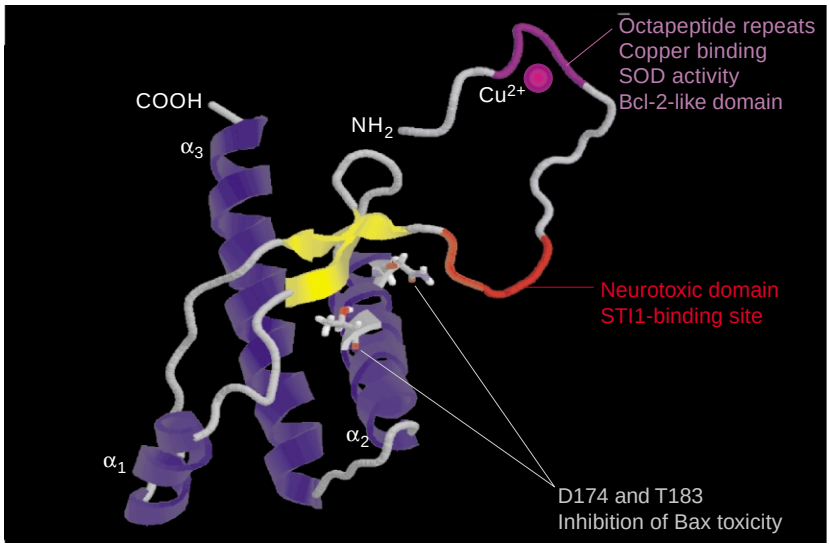

Fig. 2. The nuclear magnetic resonance (NMR) structure of the bovine prion protein (23–230), indicating the protein regions associated with activities of the normal prion protein (PrP^C). Different domains are involved in several cellular functions. The N-terminal region, in which five octapeptide repeats are located, is shown in pink. This domain has been associated with copper binding, superoxide dismutase (SOD) activity, and protection from oxidative stress and Bax-induced apoptosis. The neurotoxic domain (residues 106–126) (red) is involved in the interaction with stress-inducible protein 1 (STI1) and in the initiation of protein kinase A and extracellular-signal-regulated kinase signaling. In the C-terminal region, the amino acids D174 and T183 are associated with inhibition of Bax-induced cell death.

should help to clarify whether this form is an irrelevant by-product or a triggering factor in neurodegeneration.

Recently, it was reported that cells overexpressing *Prnp* show cytosolic accumulation of a protease-resistant PrP^{Sc}-like form, as a result of retrograde transport through the ER when proteosome activity is impaired [44,45]. The mechanism involved in neuronal cell death induced by proteosome dysfunction remains to be determined. However, it is possible that proteosome failure might cause the accumulation of misfolded proteins, triggering the ER-mediated apoptotic pathway, as it has been described in models of Huntington disease [46].

Prnp-knockout animals and doppel

The hypothesis that a loss of physiological function of PrP^C might be the cause of neurodegeneration in TSE predicts that *Prnp*-knockout animals should develop neuropathological and phenotypic alterations similar to those seen in TSE-affected animals. Several knockout lines have been generated, but differences in the way gene disruption was achieved have led to conflicting conclusions [47,48]. All mice lacking PrP^C are resistant to scrapie, do not accumulate PrP^{Sc} and are not able to propagate infectivity. The first two null mice lines generated, referred to as $Prnp^{0/0}$Zurich I and $Prnp^{-/-}$ Edinburgh, were viable and had no obvious neurological problems [49,50], although some minor electrophysiological and circadian-rhythm defects were observed. By contrast, three knockout lines generated subsequently, termed $Prnp^{-/-}$ Nagasaki, Rmc0 and $Prnp^{0/0}$Zurich II, showed cerebellar Purkinje cell degeneration and demyelination of peripheral nerves, leading to late-onset ataxia [47,51,52]. This phenotype was abolished by introduction of a *Prnp* transgene, suggesting that a loss of PrP^C activity was responsible for neurodegeneration in these animals.

The phenotypic discrepancy between the different *Prnp*-null animals was resolved by a detailed comparison of the methods by which the *Prnp* gene was disrupted [47,52]. This analysis led to the discovery of *Prnd*, a gene located downstream of PrP, which encodes the 179-residues protein Doppel (Dpl) [52]. Dpl has sequence and structural homology with the C-terminal two-thirds of PrP^C, but lacks the unordered N-terminal region. Like PrP^C, it is attached to the cell surface through a GPI-anchor [53]. The *Prnd* gene is expressed at high levels in testis and some peripheral organs, but in very low amounts in adult brain [54]. Mice carrying a homozygous disruption of the *Prnd* gene have a normal embryonic and postnatal development, but males are sterile [55].

In the *Prnp*-null animals that developed ataxia, an artefactual intergenic splicing places *Prnd* under the control of the PrP promoter, leading to high levels of Dpl in the brain. The onset of ataxia and Purkinje cell loss is directly dependent on this increase in Dpl in the central nervous system (CNS) [47,48,56], and thus neurodegeneration in these animals is apparently the result of a neurotoxic activity of Dpl, rather than the loss of a putative PrP^C neuroprotective activity. These findings led to the suggestion that some of the TSE clinical symptoms, such as ataxia, might be due to increased or unscheduled expression and activity of Dpl in brain during the disease. This possibility was investigated by grafting *Prnd*-null embryonic stem cells into wild-type mice brain and studying TSE pathogenesis in the resulting strain. The results indicated that Dpl deficiency does not prevent prion pathogenesis [57]. This conclusion is supported by a recent study showing that TSE infection does not alter the levels of *Prnd* in the CNS and that Dpl levels in the brain have no influence on incubation period, spongiform degeneration or PrP^{Sc} deposition in TSE-infected mice

[58]. Thus, it seems that expression of *Prnd* in brain does not contribute to TSE pathogenesis. However, a role for Dpl in peripheral prion replication and neuroinvasion cannot be ruled out, especially considering that *Prnd* is expressed in spleen, an organ implicated in peripheral prion pathogenesis.

The molecular mechanism by which overexpression of *Prnd* in the brain leads to cerebellar degeneration is a subject of current investigation. In the Nagazaki and Zurich II *Prnp*-null mice, Dpl neurotoxicity was rescued by introduction of a *Prnp* transgene, suggesting that PrP^C can antagonize Dpl activity and that the absence of PrP^C is a necessary prerequisite for Dpl to induce cell death [47,48,56]. Interestingly, a previous study showed that expression of a truncated PrP molecule lacking the fragment 32–134 or 32–121 of PrP (but not smaller fragments), in the Zurich I mouse background results in ataxia and degeneration of the cerebellar granule cell layer [59]. Moreover, this phenotype could be abolished by the re-introduction of a single wild-type *Prnp* allele. The truncated transgene in these experiments lacks the region of PrP^C that is also absent in Dpl, and hence it is tempting to speculate that Dpl and truncated PrP induce neurodegeneration by a similar mechanism.

Three different hypotheses have been proposed to explain the mechanism by which PrP^C antagonizes Dpl neurotoxicity [48]. First, PrP^C and Dpl might compete for interaction with an unknown receptor or ligand that promotes neuronal survival, and whereas PrP^C has a higher affinity and acts as an agonist, Dpl behaves as an antagonist because its binding is weak or incomplete. Only in the absence of PrP^C is Dpl able to bind the ligand, resulting in neurotoxicity because an inactive complex is formed, which is either unable to elicit a survival signal or triggers apoptosis. In the presence of PrP^C, the higher affinity of the ligand for its natural partner prevents the interaction with Dpl and the consequent neurotoxicity. In the absence of both PrP^C and Dpl in the brain, binding sites on the ligand remain unoccupied in which case it is necessary to postulate that either the ligand itself has an intrinsic ability to signal survival or else another hypothetical protein, previously dubbed π, is able to bind and exert PrP^C-like function [59]. This would explain why *Prnp*-knockout mice show no phenotype [59]. According to this model, PrP^C and Dpl act through the same receptor–ligand, but with opposite effects.

A second possibility is that PrP^C normally has a neuroprotective activity, whereas Dpl expressed in the brain generates a pro-apoptotic stimulus. In the absence of PrP^C, Dpl leads to cell loss and ataxia, but this effect of Dpl is suppressed in the presence of the neuroprotective activity of PrP^C. In this model, the binding partners of PrP^C and Dpl are postulated to be different and the effects generated are independent. It supports the idea that the physiological function of PrP^C is related to neuronal survival, but given the mild phenotype of the *Prnp*-null mice, this function is perhaps manifest only in the presence of injury or an apoptotic stimulus. This model explains less well why the phenotype associated with expression of truncated PrP^C resembles that resulting from expression of *Prnd*.

A third model proposes that *Prnd* expression in the brain results in a gain of a neurotoxic activity through an intrinsic amyloidogenic tendency to oligomerize, and that PrP^C re-introduced into the brain becomes part of the oligomer, making it inactive or unstable. In this hypothesis, the amyloid-like properties of Dpl are manifest only when it is expressed in its nonphysiological location, and PrP^C acts as a *trans*-suppressor of protein aggregation.

Drawing some of these ideas together, we propose an alternative model in which PrP^C has two different functional domains: a neuroprotective domain located within the N-terminal fragment of PrP and a neurotoxic domain within the C-terminal region of the protein. A balance between the two opposite activities of PrP^C might explain both the biological function of the protein and its implication in TSE pathogenesis. Under physiological conditions, the neuroprotective activity prevails, because the neurotoxic sequence is masked inside the protein, whereas during TSE pathogenesis, the protein conformational changes expose the neurotoxic domain and perhaps also inhibit the neuroprotective function, leading to neuronal apoptosis. Because Dpl and truncated PrP contain only the C-terminal domain, their expression in the absence of PrP^C leads to neurodegeneration, which is minimized by the neuroprotective effect of PrP^C when PrP^c is re-introduced into the brain. In the absence of both Dpl and PrP^C, the neuroprotective and neurotoxic activities of the protein are balanced, resulting in no obvious phenotypic changes other than hypersensitivity of the animals to apoptotic stimuli and oxidative stress. This model is consistent with evidence showing that the multiple activities of PrP are associated with different regions of the molecule (Fig. 2), which could potentially activate counteracting signaling pathways. Furthermore, it does not impose the need to postulate unknown ligands or compensatory mechanisms. A prediction of this hypothesis is that Dpl toxicity and perhaps TSE neurodegeneration might be decreased by overexpression of the N-terminal fragment of PrP.

Taken together, the data from knockout mice suggest that animals lacking PrP^C develop normally and do not exhibit major phenotypic changes that might give a clear indication of the physiological function of PrP^C. This could result from the activation of feedback compensatory mechanisms during development or might be because the alterations are too subtle to produce neurodegeneration or other overt clinical signs. To assess the possibility of compensatory mechanisms during development, a conditional postnatal $Prnp^{-/-}$ knockout mouse has been generated [60]. These mice remain healthy with no evidence of neurodegeneration or other histopathological changes for up to 15 months post-knockout. However, neurophysiological evaluation showed a significant reduction of afterhyperpolarization potentials in hippocampal CA1 cells, suggesting a direct role for PrP in the modulation of neuronal excitability. The authors concluded that acute depletion of PrP does not affect neuronal survival in this model, and ruled out loss of PrP function as a cause of TSE [60]. In spite of this, Chiarini and co-workers speculate that short-term compensation in the postnatal knockout mice could attenuate the consequences

of acute deletion of PrP^C [19]. In addition, the possibility that PrP^C deletion leads to more subtle changes that do not result in extensive neurodegeneration is supported by the results of a more detailed biochemical analysis of *Prnp*-knockout mice [61]. This study showed the presence of several markers of oxidative stress and the animals were more sensitive to neurological damage. No tissue degeneration was observed, but cells derived from these animals were hypersensitive to oxidative stress. The biochemical changes observed in these mice include increased levels of nuclear factor κB and Mn-dismutase, decreased levels of p53, altered melatonin levels, and increased levels of the apoptosis-related proteins Bax and Bcl-2 and of phosphorylated ERKs [61]. These results are consistent with the proposal that PrP^C participates in a neuroprotective signaling pathway, but that PrP^C deficiency does not lead to damage unless an external toxic stimulus is present. According to this scenario, we could speculate that TSEs arise from the combination of a toxic activity of PrP^{Sc} exacerbated by the loss of the neuroprotective activity of PrP^C.

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Conclusions and perspectives

In this article, we have discussed some of the most recent efforts to understand the biological function of the normal prion protein and its relation to TSEs. Most of the research in the field has focused on understanding the nature of the infectious agent and the mechanism by which a possible gain of neurotoxic activity of PrP^{Sc} contributes to TSE neurodegeneration. However, a more complete understanding of PrP^C-mediated signaling and its participation in the maintenance of neuronal activity is key to understanding whether a loss of function of PrP^C might have a role in the pathogenesis of prion disorders. Resolving this question is crucial for the development of therapeutic approaches to TSEs, because if reduced PrP^C physiological function is involved in disease progression, then strategies directed towards maintaining or replacing this activity could provide novel opportunities for treatment of prion-related diseases. Currently available data suggest that although PrP^C might be implicated in neuronal function and survival, it is unlikely that TSE neurodegeneration is explained exclusively by a loss of PrP^C activity.

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