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Unraveling the neuroprotective mechanisms of PrP^C in excitotoxicity

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Knowledge of the natural roles of cellular prion protein (PrP^C) is essential to an understanding of the molecular basis of prion pathologies. This GPI-anchored protein has been described in synaptic contacts, and loss of its synaptic function in complex systems may contribute to the synaptic loss and neuronal degeneration observed in prionopathy. In addition, *Prnp* knockout mice show enhanced susceptibility to several excitotoxic insults, $GABA_A$ receptor-mediated fast inhibition was weakened, LTP was modified and cellular stress increased. Although little is known about how PrP^C exerts its function at the synapse or the downstream events leading to PrP^C-mediated neuroprotection against excitotoxic insults, PrP^C has recently been reported to interact with two glutamate receptor subunits (NR2D and GluR6/7). In both cases the presence of PrP^C blocks the neurotoxicity induced by NMDA and Kainate respectively. Furthermore, signals for seizure and neuronal cell death in response to Kainate in *Prnp* knockout mouse are associated with JNK3 activity, through enhancing the interaction of GluR6 with PSD-95. In combination with previous data, these results shed light on the molecular mechanisms behind the role of PrP^C in excitotoxicity. Future experimental approaches are suggested and discussed.

Keywords: prion protein, excitotoxicity, neuroprotection, glutamate receptors, synapse, prionopathy

Abbreviations: CJD, Creutzfeldt-Jakob disease; AD, Alzheimer disease; PD, parkinson disease; HD, Huntington disease; NMDA, N-methyl-D-aspartic acid; GABA, gamma-aminobutyric acid; NR2, NMDA receptor subunit 2; GluR, glutamate receptor; PSD-95, post-synaptic density protein 95; LTP, long term potentiation; OR, octorepeat region; CNS, central nervous system; GPI, glycosyl-phosphatidylinositol; JNK, c-Jun N-terminal kinase

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The Cellular Prion Protein: The Quest for a Natural Function

The cellular prion protein is encoded by a single-copy gene (*PRNP*) that comprises two to three exons, with the open reading frame (ORF) lying in the third exon.[1,2] The resulting protein is a glycosyl phosphatidyl inositol (GPI)-anchored cell-surface glycoprotein.[3] PrP^C is highly expressed in the adult central nervous system (CNS) by post-mitotic neurons and glial cells.[4-7] Outside the CNS, elevated PrP^C expression has been reported in different cell types, such as bone marrow hematopoietic stem cells, spermatogonia or lymphocytes.[8-11] Pioneer studies reported that cultured neurons lacking PrP^C showed poor resistance to serum withdrawal,[12] and especial sensitivity to oxidative stress stimuli.[13] Thus, in order to determine the physiological functions of the protein, several cell lines lacking PrP^C expression were generated by homologous recombination in embryonic stem (ES) cells by modifications restricted to the ORF or, alternatively, by deleting the ORF but also expanding flanking regions. Using the first mouse strains homozygous for the inactivated gene (such as Zürich I.[14] or Edinburgh[15]) researchers found that these were resistant to prion infection and showed normal development. In aging mice they detected certain peripheral nervous system degeneration, albeit without clear clinical symptoms.[16] However, further detailed physiological studies reported that $Prnp^{0/0}$ mice showed weak $GABA_A$ receptor-mediated fast inhibition, modified LTP and alterations in circadian activity and sleep rhythms.[17-20] Mice carrying larger deletions overexpress Doopel (Dpl) but develop normally at perinatal stages. However, they exhibit severe ataxia and Purkinje cell loss at young-adult stages, a phenotype that can be overcome by the inclusion of a single copy of *Prnp*.[21]

In recent years, several mice lacking particular regions of PrP^C have been developed, which unveiled specific functional regions of PrP^C relevant to fast degeneration of cerebellar cells (reviewed in refs. 22 and 23). However, here we focus on some recently determined functions of PrP^C, especially related to its putative participation in synaptic plasticity and in the prevention of excitotoxicity. Although this review focuses on neurons, we should not forget that PrP^C expressed in astrocytes may have a functional influence in vivo.[24]

Histochemical analysis revealed that PrP^C is located in axons, for example in hippocampal mossy fibers.[25] However, electron microscopy analysis identified it in synaptic contacts (at both pre- and post-synaptic level).[26] In addition, loss of PrP^C function at synapses following deletion of the *Prnp* gene triggers several neural dysfunctions (see above). From a neurological point of view, prionopathies were characterized as synaptic diseases.[27] Indeed, in CJD, an abnormal form of PrP^C accumulates at synaptic terminals,[28] and physiological PrP^C function is lost. Several authors consider this as showing simply that physiological processes in prionopathies such as CJD are the result of the increased pathological effects of the misfolded protein PrP^{SC} together with the loss of natural functions of the decreased PrP^C. However, additional knowledge is needed to ascertain whether this scenario is as simple as hypothesized. We cannot rule out factors identified in recent studies that may condition the evolution of the illness: for example, the emerging role of the oligomeric or soluble forms of PrP^{SC},[29,30] the *Prnp* and non-*Prnp* genetic influence[31] changes in gene expression in affected individuals,[32] new data on the intracellular trafficking of the protein and conformational studies,[33,34] as well as the crosstalk of prionopathies with other diseases such as AD.[35,36] We need to integrate this emerging knowledge from animal models with clinical data from patients.

PrP^C and "Partners": A Scenario with Many Actors at the Synapse

Epilepsy. The first physiological descriptions mainly focused on stress and the sensitive phenotype of mutant mice.[37] Later studies indicate that *Prnp* knockout mice showed cognitive deficits, depressive-like behavior and anxiety-related responses.[38-40] Taken together, these results point to modified or unbalanced neurotransmission. Indeed, a pioneer study by Walz et al. demonstrated that mice devoid of PrP^C were more sensitive to kainate, pentylenetetrazol (PTZ) and pilocarpine injections.[41] This result was further corroborated by other authors.[18,42-45] However, a recent study using cultured slices containing zero-magnesium, bicuculline and PTZ as convulsants showed that higher concentrations of convulsants were necessary to generate spontaneous epileptiform activity in $Prnp^{o/o}$ slices in contrast to wild-type mice.[46] Moreover, we cannot rule out the possibility that other factors (e.g., genetic background, age at analysis and technical conditions) may affect the enhanced epileptic phenotype displayed for the mutant mice. These factors may also correlate with neuroanatomical modifications in the hippocampus (e.g., mossy fiber reorganization in the dentate gyrus) (reviewed in ref. 47).

But we should be cautious in extrapolating these results to CJD patients displaying different degrees of seizures, ranging from episodes of periodic lateralized epileptiform complexes (PLEDs), general status epilepticus or epilepsia partialis continua (EPC).[48-50] Readers are referred to a recent study on CJD and status epilepticus.[51]

Role of PrP^C in long-term potentiation: a challenging puzzle. Results from electrophysiological studies in *Prnp* knockout mice, which have been extensively used to examine PrP^C-mediated synaptic plasticity, have also brought controversy to the field. Several authors established that PrP^C participates in LTP in hippocampal slices,[17,19,52] and in vivo in anesthetized mice.[53,54] Collinge et al. observed that hippocampal slices from *Prnp* knockout mice have weakened $GABA_A$ receptor-mediated fast inhibition and impaired long-term potentiation.[17] A lower threshold for generating LTP in the hippocampal dentate gyrus, in *Prnp* knockout mice compared with wild-type animals, was also observed by Maglio et al.[19] In addition, Curtis et al. found a reduction in the level of post-tetanic potentiation and LTP in the CA1 region of aged *Prnp* knockout mice but not in young animals.[53] Later, the same authors reported similar results with aged *Prnp* knockout animals (9 mo old).[52] In agreement with this, we also observed enhanced synaptic facilitation in paired-pulse experiments and hippocampal LTP in living, behaving mutant mice.[54] However, Lledó et al. found no differences in LTP between control and *Prnp* knockout mice in the CA1 region of the hippocampus, although the same laboratory found a range of synaptic responses correlated with the level of PrP^C expression.[55,56] In addition, most authors attribute differences in electrophysiological recording in slice experiments between several reports vs. in vivo analysis to differences in experimental conditions.

Can PrP^C Partners be Responsible for the Differences in Observations of PrP^C Roles in Neurotransmission?

There is controversy as to whether PrP^C participates in synaptic transmission. In fact two lines of inquiry are being followed in an attempt to resolve the issue: (1) the interaction of PrP^C with extracellular elements (e.g., ions, molecules or contra-receptors) or (2) its interactions with the synaptic molecules or members of the vesicle transport machinery. In the last few years an emerging third line of analysis appears to indicate that PrP^C may modulate neurotransmission by interacting with neurotransmitter receptors.

Extracellular partners. PrP^C, which binds copper through its octarepeat domain, has been implicated in the maintenance of the redox stage at pre-synaptic level through the regulation of calcium flux.[57,58] A second example of extracellular partners can be seen by analyzing the binding of PrP^C to adhesion molecules, such as NCAM,[59,60] or laminin.[61] Binding of laminin to PrP^C modulates neuronal plasticity and memory by acting through Group I metabotropic glutamate receptors.[61]

The third and probably the most exciting example, found in 2009 in a study by Strittmatter's group, indicates that PrP^C mediates impairment of synaptic plasticity by Aβ oligomers (ADDLs).[62] Indeed, in the same study a removal function of free ADDLs was suggested for PrP^C, although

further studies by the same group failed to find a direct effect of PrP^C expression on Aβ deposition in mouse models.[63] However, the results of the same study reinforce the notion that interaction between PrP^C and ADDLs is required for suppression of synaptic plasticity in hippocampal slices.[63] In fact, a recent study reported that ADDLs increased the presence of PrP^C at the cell membrane and that to some extent the effects of intracellular ADDLs are mediated by PrP^C.[64] This contrasts with those reported by Aguzzi's group, who found no change in the impairment of hippocampal synaptic plasticity in a transgenic model of AD after *Prnp* deletion or overexpression, suggesting that PrP^C has a weak role as mediator of Aβ toxicity.[35] Indeed, no changes in PrP^C protein levels were detected in AD patients,[65] although fibrillar forms of PrP^C and Aβ are detected in amyloid plaques,[66] and fibrillar forms of PrP^C and Aβ interact in AD brains.[67]

We conclude that the pathophysiological relevance of the PrP^C/Aβ interaction remains to be established.

Intracellular partners. PrP^C may participate in neurotransmitter release, as reported at the neuromuscular junction, by interacting with synaptic associated proteins.[68] Indeed, Synapsin Ib and Synaptophysin (among others) have been reported to interact with PrP^C (reviewed in ref. 69). In fact, misfolded PrP^C has been implicated in SNARE dysfunction in vitro (see below), but surprisingly, not in vivo.[70] Again parallels are found between bench experiments and CJD patients, since defective synaptic machinery in infected brains (mainly (SNAP-25), syntaxin-1 and synapsin-1) was demonstrated several years ago.[27,71] However, whether these changes affect the symptoms and the evolution of the illness requires additional study. In this regard, recent approaches analyzing gene expression changes in different rodent models lacking PrP^C,[18,72] and the comparison with CJD patients and prion infected animals[73-76] could be of interest in order to harmonize data. On the other hand, a large group of PrP^C-binding proteins locate into vesicles or caveolae-like domains such as Casein Kinase 2, Caveolin-1, Grb-2, p75 and Pint-1 (reviewed in ref. 77). Recently, an interaction between PrP^C and Rab7 has also been shown, and silencing of Rab7a promotes PrP^C accumulation in Rab9-positive endosomal compartments,[78] which implicates PrP^C in vesicular trafficking. The potential effects of these interactions in lipid rafts and associated vesicles on vesicular trafficking, cellular signaling and neuroprotection warrants further study. A scheme summarizing proposed functional interactions for PrP^C at the cell membrane is shown in **Figure 1**.

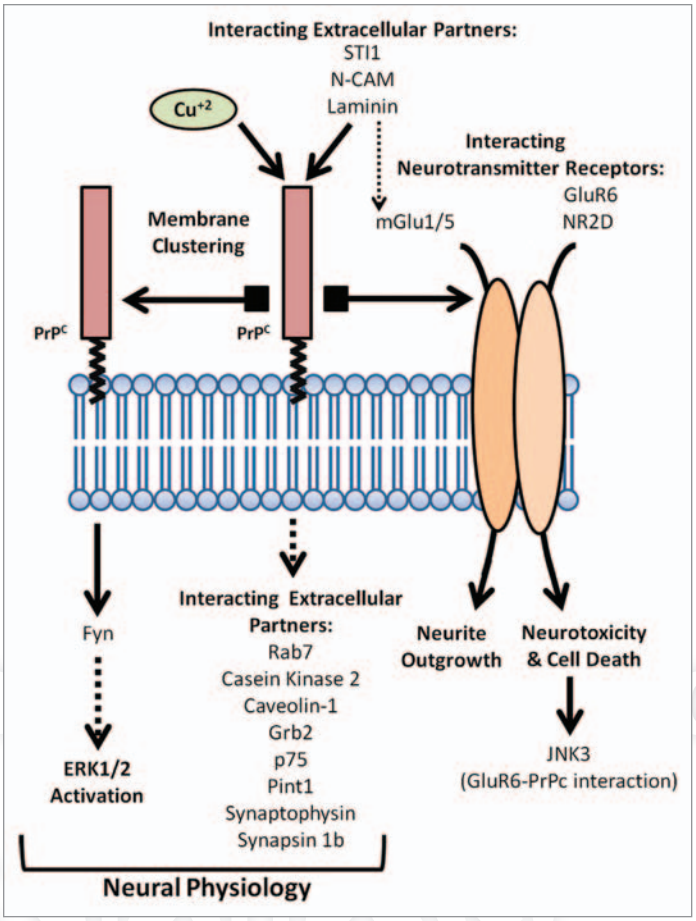

Figure 1. Scheme of the proposed functional roles for PrP^C at the cell membrane as intracellular transducer of extracellular signals. PrP^C mediates self-aggregation, interaction with intracellular and extracellular partners or with glutamatergic receptor subunits, leading to a broad range of molecular mechanisms regulating neuronal cell physiology.

Emerging Roles of PrP^C: Modulating Neurotransmitter Receptors in Intracellular Processes in Excitotoxicity

The signaling mechanism that triggers PrP^C remains elusive. After antibody recruitment of PrP^C at the plasma membrane, Fyn,[60,79-81] and ERK/CREB signaling activation has been described.[82,83] However, PrP^C aggregation by specific antibodies also leads to cell death by increased ROS in vitro and in vivo,[84,85] which raises the question of whether this is the natural mechanism of PrP^C-mediated signaling (reviewed in ref. 47). Although it is assumed that PrP^C transduces neuroprotective signals,[86] we should not consider it as a generic neuroprotective molecule per se.[87] In fact, Steele et al. showed that deletion of *Prnp* in several transgenic models of neurodegenerative disease (PD, HD, tauopathy) did not contribute to the development of the disease, suggesting a context-dependent neuroprotective function for PrP^C.[88] As indicated above, the enhanced susceptibility of *Prnp* knockout to glutamate excitotoxicity has been reported extensively.[41,42,89] In addition, neuronal cell death in the hippocampus of *Prnp* knockout mice has been described in response to glutamate

toxicity when compared with control animals.[42,45] In addition, Koshravani et al. recently measured NMDAR-mediated currents and mEPSCs recorded from *Prnp* knockout hippocampal slices and showed events with significantly larger amplitudes than those observed in control animals.[45] Furthermore, NMDAR-mediated mEPSCs of *Prnp* knockout slices showed significantly longer decay times.[45]

However, little is known about the molecular mechanisms activated by the lack of PrP^C in the presence of excitotoxic insults. When compared with control mice, we observed increased phospho-JNK reactivity in the pyramidal cells of the hippocampal CA1 and enhanced sensitivity to seizures and hippocampal cell death.[42] Further, we investigated the signaling pathways activated after KA treatment in the *Prnp* knockout mice.[44]

PrP^C, Glutamate Receptors and JNK3 Activity

JNK has been implicated in several neurodegenerative diseases such as AD and PD,[90,91] and it plays a crucial role in epilepsy and stroke.[92,93] Of the three isoforms of JNK (JNK1, 2 and 3), JNK3 was a good candidate to be a key molecule in the PrP^C-dependent transmission of the excitotoxicity provoked by glutamate: (1) JNK3 is predominantly expressed in the CNS;[94] (2) *Jnk3* knockout provides neuroprotection against various injuries,[95,96] and most interestingly, resistance to epileptic seizures and hippocampal cell death;[92] and (3) the JNK3 apoptotic signaling pathway is reported to be induced by KA and ischemia.[92,97] With these results in mind, we recently generated a double knockout mutant *Prnp/Jnk3,* which was insensitive to seizure and hippocampal cell death in response to KA injections.[44] This observation was corroborated in organotypic slices using pharmacological JNK inhibitors.

On the other hand, several authors reported that assembly of the GluR6-PSD-95-MLK3 trimer induced by KA and ischemia is essential for the activation of JNK3.[98,99] JNK3 phosphorylation and activation induces phosphorylation of c-Jun, which is part of the AP-1 complex. The JNK-c-Jun-AP-1 pathway plays a key role in cell death and apoptosis regulation following several insults. Interestingly, GluR6, JNK3 and c-Jun $Ser^{63/73AA}$ knockout mice are resistant to KA-induced seizures.[92,100,101] We observed that PrP^C favors the interaction between GluR6 and PSD-95 in the presence of KA, and that PrP^C interacts with GluR6-PSD-95 in the PSD fraction from hippocampus.[44]

In this regard, interaction between PrP^C and NR2D was also observed by Khosravani et al. Similarly to our observations, the presence of PrP^C silenced NR2D and reduced excitotoxic lesions in the presence of NMDA. In addition, Group I metabotropic glutamate receptors (mGluR1/5) also associate with PrP^C. Furthermore, Group I mGluRs are involved in the transduction of cellular signals triggered by PrP^C-Laminin interaction.[61]

PrP^C and Excitotoxicity: New Questions

As in any other scientific field, a particular discovery may raise more than a hundred challenging questions. Current data indicate that PrP^C contributes to a general neuroprotective mechanism in response to excitotoxic insults through interaction with glutaminergic receptors. However, we first need to establish whether this neuroprotective response of PrP^C to increased glutamate is pleiotropic or specific to a particular subset of glutamate receptors. In order to determine whether PrP^C inhibits the glutamate-mediated post-synaptic hyperexcitation of neural cells in a specific manner, further interactome experiments from post-synaptic density-enriched fractions should be performed. In this regard Khosravani et al. demonstrated some degree of specificity between PrP^C and NMDAR subunits, since they did not detect NR2B in their PrP^C immunoprecipitates.[45] In addition, it would also be interesting to study the kinetics of the interaction between PrP^C and its receptor partners in order to establish the role of PrP^C under basal conditions. To date, several interactome studies have been performed in neuroblastoma cell lines over-expressing PrP^C or in transgenic myc-PrP mice.[78,102,103] Although the list of PrP^C interacting partners is increasing, the main problem so far resides in our lack of knowledge of the functional relevance of these interactions.[104] We can find some exceptions such as the interaction of PrP^C with the plasma membrane stress-inducible protein 1 (STI1) that has clearly been shown to transduce extracellular signals to the intracellular environment of PrP^C expressing cells in an alpha7 nicotinic acetylcholine receptor-dependent manner.[105-107]

Another open question in this field is how PrP^C inhibits GluR6 and NR2D. Khosravani and Steele hypothesized, for the NR2D-PrP^C interaction, that PrP^C could block receptor agonist binding, stabilize the closed state of the channel, or act indirectly by interfering with signaling pathways affecting glutamate receptor functions by individual regulation of its subunits.[45,108] Mapping the interaction regions between PrP^C and GluR6 and NR2D may help to discern the molecular mechanisms by which PrP^C silences both receptor subunits. In addition, since GPI seems to play an essential role in the physiological and pathological functionality of PrP^C [109,110] the PrP^C-GPI domain may help to direct the interaction between PrP^C and glutamate receptor subunits. In this regard, interaction and neurotoxic experiments with the anchorless *Prnp* transgenic mice ($GPI^{-/-}$), which produces a PrP^C form that is mainly released in the culture media in a fully glycosylated, soluble form, could be a good approach to this issue.

Final Remarks

Despite efforts to discern the physiological role of PrP^C, understanding its biological function presents several challenges. There are a large number of PrP^C-partners, most of which still need to be associated with a biological function. In addition, the pleiotropic phenotypes of the various *Prnp* knockout mice hinder the study of basic biological PrP^C-dependent functions. Furthermore, our lack of knowledge of the PrP^C-dependent signaling pathways, both in physiological and in pathological conditions, makes it difficult to integrate the biological information gathered from membrane (receptor) levels to gene expression. The development of new experimental tools such as double

JNK3-glutamatergic subunit knockout mice, together with the discovery of new potential PrP^C partners involved in neurotransmission, and the study of such interactions using interdisciplinary approaches (merging data from proteomic, cell signaling and neuropathological experiments) may help to elucidate the neuroprotective role of PrP^C in response to excitotoxic insults.

Finally, although a striking degree of conservation between the *Prnp* mammalian sequences has been observed, to date there are no studies linking PrP^C-mediated excitotoxicity at the evolutionary level. However, the contribution of recent articles on the structural differences between different species may bring some light on how these changes may be crucial for the PrP^C physiology.

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