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Is, indeed, the prion protein a Harlequin servant of "many" masters?

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Tens of putative interacting partners of the cellular prion protein (PrP^C) have been identified, yet the physiologic role of PrP^C remains unclear. For the first time, however, a recent paper has demonstrated that the absence of PrP^C produces a lethal phenotype. Starting from this evidence, here we discuss the validity of past and more recent literature supporting that, as part of protein platforms at the cell surface, PrP^C may bridge extracellular matrix molecules and/or membrane proteins to intracellular signaling pathways.

Initially, the discovery that the prion protein was the major, if not the unique, component of the prion agent causing transmissible spongiform encephalopathies (TSE)[1] has placed the protein in an extremely unfavorable light. Thereafter, however, a wealth of evidence has supported the notion that the protein positively influences several aspects of the cell physiology, and that its duality—in harboring both lethal and beneficial potentials—could be rationalized in terms of a structural switch. Indeed, the protein exists in at least two conformational states: the cellular, α helix-rich isoform, PrP^C, and the prion-associated β sheet-rich isoform, PrP^{Sc}.[2] If it is now unquestionable that the presence of PrP^C in the cell is mandatory for prion replication and neurotoxicity to occur,[3,4] nonetheless its physiologic function is still debatable, despite the long lasting effort, and the numerous, frequently genetically advanced, animal and cell model systems dedicated to the issue. From these studies the picture of an extremely versatile protein has emerged, whereby PrP^C acts in the cell defense against oxidative and apoptotic challenges, but also in cell adhesion, proliferation and differentiation, and in synaptic plasticity.[5,6] In an effort to converge these multiple propositions in an unifying functional model, different murine lines devoid of PrP^C have been studied. These animals, however, displayed no obvious phenotype,[7-9] suggesting that either PrP^C is dispensable during development and adult life or that compensative mechanisms mask the loss of PrP^C function in these paradigms. Thus, identifying the exact role of PrP^C in the cell would not only resolve an important biological question, but would also help elucidate the cellular steps of prion pathogenesis necessary for designing early diagnostic tools and therapeutic strategies for TSE.

As is often the case, the employment of a model system unprecedented in prion research has recently disclosed a most interesting scenario with regards to PrP^C physiology, having unravelled, for the first time, a lethal phenotype linked to the absence of the protein.[10] The paradigm is the zebrafish, which expresses two PrP^C isoforms (PrP1 and PrP2). Similarly to mammalian PrP^C, they are glycosylated and attached to the external side of the plasma membrane through a glycolipid anchor. PrP1 and PrP2 are, however, expressed in distinct time frames of the zebrafish embryogenesis. Accordingly, the knockdown of the PrP1, or PrP2, gene very early in embryogenesis impaired development at different stages, bypassing putative compensatory mechanisms. By focusing on PrP1, Malaga-Trillo et al. showed that the protein was essential for cell adhesion, and that this event occurred through PrP1 homophilic trans-interactions and signaling. This comprised activation of the Src-related tyrosine (Tyr) kinase p59fyn, and, possibly, Ca^{2+} metabolism, leading to the regulation of the trafficking of E-cadherin, a member of surface-expressed cell adhesion molecules (CAMs) responsible for cell growth and differentiation.[11] It was also reported that overlapping PrP1 functions were performed by PrP^Cs from other species, while the murine PrP^C was capable to replace PrP1 in rescuing, at least in part, the knockdown developmental phenotype. Apart from providing the long-sought proof for a vital role of PrP^C, the demonstration that a mammalian isoform corrected the lethal zebrafish phenotype strongly reinforces previous results—mainly obtained in a variety of mammalian primary neurons and cell lines—pointing to a functional interplay of PrP^C with CAMs, or extra cellular matrix (ECM) proteins, and cell signaling, to promote neuritogenesis and neuronal survival. A revisit of these data is the main topic of the present minireview.

As mentioned, the capacity of PrP^C to act as a cell adhesion, or recognition, molecule, and to entertain interactions with proteins implicated in growth and survival, has already been reported for the mammalian PrP^C. A case in point is the interaction, both in cis- and trans-configurations, with the neuronal adhesion protein N-CAM12 that led to neurite outgrowth.[13] Like cadherins, N-CAM belongs to the CAM superfamily. Following homo- or heterophylic interactions, it can not only mediate adhesion of cells, or link ECM proteins to the cytoskeleton, but also act as a receptor to transduce signals ultimately resulting in modulating neurite outgrowth, neuronal survival and synaptic plasticity.[11] Another example is the binding of PrPC to laminin, an

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ECM heterotrimeric glycoprotein, which induced neuritogenesis together with neurite adhesion and maintenance,[14,15] but also learning and memory consolidation.[16] Further, it has been described that PrPC interacted with the mature 67 kDa-receptor (67LR) (and its 37 kDa-precursor) for laminin, and with glycosamminoglycans (GAGs), each of which is involved in neuronal differentiation and axon growth.[17-21] More recently, Hajj et al.[22] have reported that the direct interaction of PrP^C with another ECM protein, vitronectin, could accomplish the same process, and that the absence of PrP^C could be functionally compensated by the overexpression of integrin, another laminin receptor.[23] Incidentally, the latter finding may provide a plausible explanation for the absence of clear phenotypes in mammalian PrP-null paradigms. By exposing primary cultured neurons to recombinant PrPs, others have shown that trans-interactions of PrP^C are equally important for neuronal outgrowth,[24,25] including the formation of synaptic contacts.[25] Finally, it has been demonstrated that the binding of PrP^C with the secreted co-chaperone stress-inducible protein 1 (STI1) stimulated neuritogenesis.[26] This same interaction had also a pro-survival effect, as did the interaction of PrP^C with its recombinant form.[24] Notably, the involvement of PrP^C in cell protection has been heightened by experiments with whole animals. By applying transient or permanent focal cerebral ischemia to the animals, it was found that their reduced brain damage correlated with spontaneous or adenoviral-mediated, upregulation of PrP^C,[27-29] (reviewed in ref. 30), and that PrP^C deficiency aggravated their ischemic brain injury.[30,31] Thus, now that data are available from phylogenetically distant paradigms (zebrafish and mammalian model systems), it acquires more solid grounds the advocated engagement of PrP^C in homo/heterophilic cis/trans interactions to trigger signaling events aiming at neuronal—or, in more general terms, cell—survival and neuritogenesis. The latter notion is consistent with the delayed maturation of different types of PrP^C-less neurons, observed both in vitro and in vivo.[32,33]

If one assumes that the interaction of PrP^C with multiple partners (45 for PrP^C and PrP^{Sc}, as reviewed in Aguzzi et al.,[5] or 46 considering the homophylic interaction) are all functionally significant, the most immediate interpretation of this "sticky" behavior entails that PrP^C acts as a scaffolding protein in different membrane protein complexes.[5,6] Each complex could then activate a specific signaling pathway depending on the type and maturation of cells, the expression and glycosylation of PrP^C, and availability of extra- and intra-cellular signaling partners. At large, all these signals have been shown to be advantageous to the cell. However, because in a cell only a subtle line divides the "good" from the "bad," instances can be envisioned in which a pro-life signal turns into a pro-death signal. A typical example of this possibility is glutamate excitotoxicity resulting in dangerous, glutamate receptor-linked, Ca^{2+} overload. Likewise, an excessive or over-stimulated signal elicited by PrP^C, or by the putative complex housing the protein could become noxious to the cell. This possibility may explain why the massive expression of PrP^C caused degeneration of the nervous system,[34] and of skeletal muscles,[34,35] in transgenic animals. More intriguing is the finding that—in a mouse line expressing anchorless PrP^C—PrP^{Sc} was capable to replicate without threatening the integrity of neurons.[36] This may suggest that native membrane-bound PrP^C acts as, or takes part into, a "receptor for PrP^{Sc}", and that lasting PrP^{Sc}-PrP^C interactions distort the otherwise beneficial signal of the protein/complex and cause neurodegeneration.[37] Consistent with this hypothesis is the finding that the in vivo antibody-mediated ligation of PrP^C provoked apoptosis of the antibody-injected brain area.[38] Speculatively, the action of N-terminally, or N-proximally truncated PrPs whose expression in PrP-less transgenic mice induced extensive neurodegeneration,[39-41] may be traced back to the same hyper-activation of PrP^C signaling. Possibly, this may hold true also for the synaptic impairment that, recorded only in PrP^C-expressing neurons, was attributed to the binding of amyloid beta (Aβ) peptide oligomers implicated in Alzheimer disease, to PrP^C.[42,43]

But which is (are) the cellular signaling pathway(s) conveyed by the engagement of PrP^C in different signaling complexes? In line with its multifaceted behavior, several intracellular effectors have been proposed, including p59fyn, mitogen-activated kinases (MAPK) Erk1/2, PI3K/Akt and cAMP-PKA. p59fyn is the most reported downstream effector, suggesting that, in accordance with its behavior, p59fyn could serve as the sorting point for multiple incoming and outgoing signals also in the case of PrP^C. The initial evidence of the PrP^C-p59fyn connection came from cells subjected to antibody-mediated cross-linking of PrP^C.[44] Later, it was shown that the PrP^C-p59fyn signal converged to Erk1/2 through a pathway dependent on (but also independent of) reactive oxygen species generated by NADPH oxidase.[45] A PrP^C-dependent activation of p59fyn[13,25] and Erk1/2 (but also of PI3K and cAMP-PKA)[24] was evident in other neuronal cell paradigms and consistent with the almost ubiquitous expression of PrP^C, in non-neuronal cells such as Jurkat and T cells.[46] Not to forget that in zebrafish embryonic cells activated p59fyn was found in the same focal adhesion sites harboring PrP1.[10] Regarding the activation of the ERK1/2 pathway promoted by the PrP^C-STI1 complex, and leading to neuritogenesis, the role of p59fyn was not investigated.[26] The same holds true for the transduction of a neuroprotective signal by the PrP^C-STI1 complex involving the cAMP-PKA pathway.[26] Interestingly, this is not the only example reporting that engagement of PrP^C activates simultaneously two independent pathways. In fact, possibly after transactivating the receptor for the epidermal growth factor, the antibody-mediated clustering of PrP^C was shown to impinge on both the Erk1/2 pathway, and on a protein (stathmin) involved in controlling microtubule dynamics.[47]

Yet, if p59fyn is implicated in mammalian PrP^C-activated signaling cascade, a protein linking extracellular PrP^C to p59fyn is needed, given the attachment of the enzyme to the inner leaflet of the plasma membrane through palmitoylated/myristoylated anchors. In this, the PrP^C partner N-CAM (isoform 140) seems ideal to fulfill the task, given that p59fyn is part of N-CAM-mediated signaling. Indeed, after recruitment of N-CAM to lipid rafts—which may also depend on PrP^C,[13]—together with the receptor protein Tyr phosphatase α (RPTPα), the Tyr-phosphate removing activity of RPTPα allows the subsequent activation of p59fyn through an autophosphorylation step.[48] This event

recruits and activates the focal adhesion kinase (FAK),[11] another non-receptor Tyr kinase. Finally, formation of the FAK-p59fyn complex triggers neuritogenesis through both Erk1/2 and PI3K/Akt pathways.[49,50] Parenthetically, the FAK-p59fyn and PI3K/Akt connection would be suitable to explain why aggravation of ischemic brain injury in PrP-deficient brains was linked to a depressed Akt activation.[31] FAK-p59fyn complex, however, may be also involved in the signal triggered by the still mysterious PrP^C partner, 67LR. This protein was reported not only to act as a laminin receptor but also to facilitate the interaction of laminin with integrins,[51] thereby possibly activating (through integrins) FAK-p59fyn-regulated pathways.[49] Conversely, other data have supported the candidature of caveolin-1 for coordinating the signal that from PrP^C reaches Erk1/2 through p59fyn.[44,45,52] Further scrutiny of this route has shown that it comprised players such as laminin and integrins (upstream), FAK-p59fyn, paxillin and the Src-homology-2 domain containing adaptor protein (downstream), and that caveolin-1, a substrate of the FAK-p59fyn complex, facilitated the interaction of these signaling partners by recruiting them in caveolae-like membrane domains.[53]

For the relevance they bear, we need to acknowledge recent propositions supporting the commitment of PrP^C with proteins whose function is unrelated from the above-mentioned cell adhesion or ECM molecules; namely, the β-site amyloid precursor protein (APP) cleaving enzime (BACE1) and the N-methyl-D-aspartate (NMDA)-receptor. BACE1 is a proteolytic enzyme involved in Aβ production. It has been shown that overexpressed PrP^C restricted, while depletion of PrP^C increased the access of BACE1 to APP, possibly because PrP^C interacts with BACE1 via GAGs.[54] Thus, native PrP^C reduces the production of Aβ peptides. A beneficial effect of PrP^C was also highlighted by Khosravani et al.[55] showing that, by physically associating with the subunit 2D of the NMDA-receptor, PrP^C attenuated neuronal Ca^{2+} entry and its possible excitotoxic effect. This clear example for the control of PrP^C on Ca^{2+} metabolism is particularly intriguing in light of previous reports linking Ca^{2+} homeostasis to PrP^C pathophysiology (reviewed in ref. 56). Also, it is important to mention that a few partners of PrP^C or downstream effectors may initiate signals that increase intracellular Ca^{2+}, and that, in turn, local Ca^{2+} fluctuations regulate some of the afore-mentioned pathways.[11,49,57,58]

In conclusion, although still somehow speculative, the implication of Ca^{2+} in PrP^C-dependent pathways raises the possibility that the different input signals originating from the interaction of PrP^C with diverse partners may all converge to the universal, highly versatile Ca^{2+} signaling. Were indeed this the case, then clearly the acting of PrP^C as Harlequin, the famous character of the 18th century Venetian playwright Carlo Goldoni, who struggles to fill the orders of two masters, would be merely circumstantial.

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