Cell. Mol. Life Sci. (2012) 69:1105–1124
DOI 10.1007/s00018-011-0847-7

Cellular and Molecular Life Sciences

REVIEW

Allosteric function and dysfunction of the prion protein

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Received: 17 August 2011 / Revised: 16 September 2011 / Accepted: 20 September 2011 / Published online: 9 October 2011

Abstract Transmissible spongiform encephalopathies (TSEs) are neurodegenerative diseases associated with progressive oligo- and multimerization of the prion protein (PrP^C), its conformational conversion, aggregation and precipitation. We recently proposed that PrP^C serves as a cell surface scaffold protein for a variety of signaling modules, the effects of which translate into wide-range functional consequences. Here we review evidence for allosteric functions of PrP^C, which constitute a common property of scaffold proteins. The available data suggest that allosteric effects among PrP^C and its partners are involved in the assembly of multi-component signaling modules at the cell surface, impose upon both physiological and pathological conformational responses of PrP^C, and that allosteric dysfunction of PrP^C has the potential to entail progressive signal corruption. These properties may be germane both to physiological roles of PrP^C, as well as to the pathogenesis of the TSEs and other degenerative/non-communicable diseases.

Keywords Prion · Scaffold proteins · Signal transduction · Neurodegeneration · Cell surface · Oligomerization · Signaling modules

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Introduction

The prion protein (PrP^C) was discovered and characterized amid the search for the infectious pathogen involved in the transmissible spongiform encephalopathies (TSEs), a family of severe, still incurable and invariably fatal neurodegenerative diseases [1, 2]. Studies of the pathogenesis of TSEs pointed to the central role of an abnormal conformer of PrP^C because of changes in the secondary structure of this protein [1, 3]. The infectious pathogen was designated *prion*, an acronym for *proteinaceous infectious only*, after which PrP^C was named, and that also led to the alternative term 'prion diseases' to denominate TSEs [4].

The cognitive and motor signs and symptoms of the TSEs are attributed to progressive neurodegeneration, associated with oligo- and multimerization, aggregation, occasional amyloid fibrillization, and precipitation of the abnormal protein conformer [5, 6]. In line with present trends in Alzheimer's disease [7, 8], current thinking favors the hypothesis that TSEs are caused by protein oligomers within a certain range of sizes, on their way to eventually precipitate as the relatively large, compact deposits detectable by light microscopical examination of autopsy specimens [5, 9, 10].

Clinical assays of new treatments for prion diseases have been so far designed on the basis of robust therapeutic effects in prion-infected cell cultures, mostly related to either the prevention or disassembly of aggregates of the abnormal conformer of PrP^C. Heretofore the results have been disappointing [11–13]. A significant hurdle is the absence of reliable pathognomonic markers of the TSEs in living patients [14]. Postmortem confirmation of diagnosis is required, through the observation of end-stage spongiosis and cell death in brain tissue, together with immunohistochemical detection of compact, insoluble and protease-

resistant aggregates of the abnormal conformer of PrP^C [15]. Notably, neuron death, the immunohistopathological marker, and the neurodegenerative disease proper often do not fit together in autopsy specimens [16–18].

An additional, recurrent and frequently underappreciated issue in experimental approaches is the variability of the kinetics of formation of the aggregated, presumably toxic forms of the prion protein in vitro, and the uncertain correlation between those and the actual rates of building up their counterparts in human TSEs, or even in experimental animal models [19–26]. Survival of TSE patients is of the order of several months after diagnosis, varies among distinct forms of TSE [27, 28], and the events required to produce diagnostic symptoms are still unclear. Also, the time courses of experimental approaches may differ from those of the corresponding TSEs by several orders of magnitude. It is, therefore, still difficult to equate human prion diseases with the corresponding animal models, not to mention the responses of cell lines to prions in vitro.

Despite significant advances in the field, fundamental questions remain unanswered [3, 29–33]. Unknown variables include the mechanisms of conformational conversion of PrP^C into prions; the events that cause neuronal dysfunction and degeneration; the signal transfer molecules that transduce the pathogenic signals derived from the progressive aggregation of toxic species; the roles of either dysfunction or death of neurons and glia in the diverse symptoms associated with TSEs; the differential topography of brain lesions associated with distinct TSEs; why specific mutations in the prion gene (*PRNP*) lead to conformational conversion; why specific mutations associate with distinct TSEs; the determinants of the so-called prion *strains*; the role, if any, of nucleic acids in the composition of prions; and last, but not least, the functional properties of the normal prion protein, together with the role of loss of its function(s) in the pathogenesis of the TSEs.

We have proposed that the prion protein functions as a cell surface scaffold for the assembly of signaling modules, based on which selective interactions with many ligands and transmembrane signaling pathways translate into wide-range consequences upon both physiology and behavior [34]. The assembly of molecular complexes both entails and depends on orchestrated allosteric structural changes propagated in the various components of the complex [35, 36], and scaffold proteins are proposed to act as allosteric effectors on their partners. Thus, they do not only allow the proximity between ligands, but may also impose on the conformation of those binding molecules, thereby affecting their activity [37]. This review attempts to provide a framework for the study of such allosteric properties of PrP^C, which may be germane both to the roles of the prion protein in physiological context, as well as to the pathogenesis of the TSEs.

Structure, topology and trafficking of the prion protein

Mammalian prion protein (Fig. 1) is found at the cell surface as a glycosylated, GPI-anchored protein of 208–209 amino acids. PrP^C contains an *N*-terminal flexible, random coil sequence comprising approximately residues 23–124, which is flexible and disordered in solution [38, 39], and a *C*-terminal globular domain of about 100 amino acids. The latter are arranged in three α-helices corresponding to residues 144–154, 173–194 and 200–228, interspersed with an antiparallel β-pleated sheet formed by β-strands at residues 128–131 and 161–164 in human PrP. A single disulfide bond connects cysteine residues 179 and 214 [39].

PrP^C can be non-, mono- or di-glycosylated with a variety of *N*-glycans in one residue contained within α-helix 2 and another between α-helices 2 and 3 [40]. Protein glycosylation reportedly affects the recognition of various species of PrP^C by monoclonal antibodies [41–43], as well as PrP^C trafficking and biophysical features [44–46].

Similar to other GPI-anchored proteins, PrP^C molecules attach to low-density, detergent-insoluble membrane domains (DRM) dubbed 'membrane rafts,' rich in cholesterol and sphingolipids [47–55]. Membrane attachment through the GPI anchor, as well as other PrP^C-membrane interactions, modulate, if only slightly, the structure of the protein [56–59].

A critical issue is that association of PrP^C with lipid rafts is highly dynamic [60]. A large fraction of the protein is found at any time in non-raft membrane, on its way to

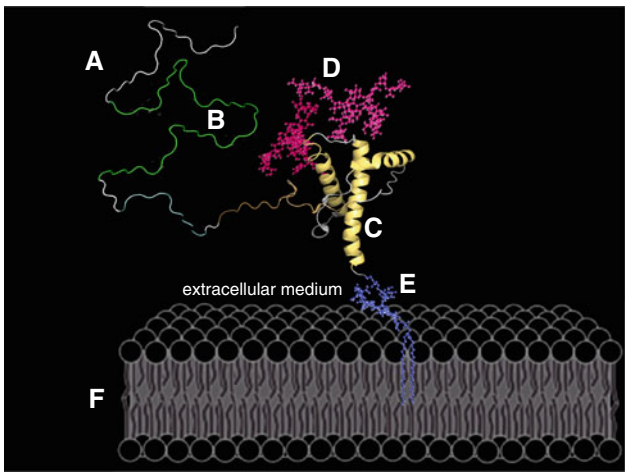

Fig. 1 The cell surface, GPI-anchored prion protein. Drawing approximately to scale of the prion protein, showing (**a**) the *N*-terminal flexible domain; (**b**) location of the octapeptide repeat domain; (**c**) the *C*-terminal globular domain; (**d**) glycosylation chains, representing a di-glycosylated form; (**e**) GPI-anchor; (**f**) plasma membrane. Amino acid sequences are described in the legend to Fig. 4. Globular domain is depicted with Pymol software, from PDB record 1XYX of mouse PrP121-231; GPI anchor and glycosylation residues are from [142]. Modified from [239]

endocytosis [61]. Conversely, cross-linking can induce the recruitment of PrP^C from a large pool of non-raft to raft membrane domains [62]. Circulation of PrP^C between the cell surface and intracellular compartments is rapid and cyclic [61], and may follow various pathways (reviewed in [34, 60]). Some of the endocytosed PrP^C is degraded by lysosomes, but most molecules return to the cell surface for several rounds of recycling. In addition, part of the recycled PrP^C may be secreted to the extracellular medium associated with exosomes derived from multi-vesicular bodies [63, 64].

The low-density lipoprotein receptor-related protein (LRP1) is required for clathrin-mediated PrP^C endocytosis in individual cells [49, 51, 65], although its role upon the trafficking of PrP^C in organized tissue is still unclear (R.J. Morris, personal communication). Other transmembrane proteins, such as the laminin receptor precursor (LRP), may also play a role in the subcellular traffic of PrP^C [66]. Endocytosis of PrP^C can be regulated by Cu^{2+} ions [67, 68], by its binding partner hop/STI1 [69], and by sulfated glycans and suramin [70, 71], as well as by antibody cross-linking [72].

Trafficking of the prion protein, particularly along endocytic pathways, allows the encounter of significant variations of local pH. It has been argued that the pH does not significantly affect the three-dimensional structure of PrP^C [73]. However, changes in pH were shown to modify the stability of the protein [74, 75], and a folding intermediate was isolated by incubation of PrP^C at acidic pH [73–76]. Previous work showed that the conformation of the *C*-terminal domain (from residue 90) of PrP^C is sensitive to pH [56, 74, 76–78]. Acidic pH also imparts changes in antibody binding in the *N*-terminal flexible domain [78]. Changes in conformation along the progressive acidification of trafficking endocytic vesicles may be relevant for functional properties of PrP^C, such as the selection of partners as well as binding affinity.

Minor truncated, transmembrane and cytosolic forms of PrP^C were described, usually following abnormal treatments or overexpression in cultured cells. Proteolytic cleavage of PrP^C may occur, and clipping usually removes the *N*-terminal region, leaving a GPI-anchored, truncated *C*-terminal domain of the protein [79]. PrP^C is also released in a soluble form [80, 81], which may be relevant for the modified disease characteristics found associated with anchorless forms of the prion protein in mice [82–84]. Still, the cell surface, GPI-anchored form constitutes almost all of PrP^C found during its normal life cycle [49].

The prion protein as a cell surface scaffold protein

Work in various laboratories showed that: (1) the engagement, cross-linking, deletion, overexpression or otherwise change in the content and distribution of PrP^C affects proliferation, differentiation, sensitivity to cell death and additional cellular properties not only of neurons, but also of other cells and tissues; (2) multiple signal transduction pathways are involved in such biological responses; (3) several metal ions, proteins, glycoconjugates and nucleic acids bind to PrP^C in either its native, normal form or in the anomalous conformation; (4) in some cases, such ligands induce PrP^C-dependent cellular responses in physiological context, and their binding sites have been mapped in both the PrP^C molecule and the ligand; (5) PrP^C undergoes multiple cycles of endocytosis and retrieval to the cell surface, before finally entering a degradation route at a relatively fast turnover rate ([34] for review).

The lack of an overt phenotype in the first reported PrP^C-null mice [85] delayed the recognition of physiological properties of the prion protein, and curtailed the hypothesis that the corruption or loss of these functions may hold important clues as to the pathogenesis of TSEs [86]. Further work, nonetheless, eventually disclosed a number of functional consequences of deletion of the prion protein [34, 87].

In particular, evidence is now compelling that the prion protein is involved in signal transduction. Early work showed that engagement of PrP^C leads to activation of the soluble tyrosine kinase Fyn, [88], and of the cyclic AMP/protein kinase A and Erk MAP kinase pathways, [89, 90]. The latter work led to the identification of hop/STI1 as a binding partner of PrP^C and the mapping of their cognate binding domains [90].

Engagement of PrP^C with hop/STI1 leads to neuroprotection through the cAMP/PKA pathway and neurite outgrowth through the ERK pathway, and endocytosis is required for the latter, but not for the former signaling event [69, 91, 92]. Thus, engagement of PrP^C leads to the activation of distinct intracellular signaling pathways with differing biological effects, similar to most membrane receptor-mediated signal transfer systems [93, 94]. A noncommittal interpretation of the functional interaction of hop/STI1 and PrP^C, thus, ascribed the role of a neurotrophic factor for the co-chaperone, whereas PrP^C may play the role of either a receptor or co-receptor for secreted hop/STI1 [95]. Similar neurotrophic effects follow the binding of PrP^C to a defined domain within the laminin gamma chain [96], as well as to vitronectin [97].

Although the physiological relevance of certain cellular responses and ligands has been challenged [98], and in some cases the topology of the presumptive ligands seems inconsistent with interactions in living cells [34], compelling evidence accumulated that PrP^C may interact with multiple partners [34, 99, 100], particularly at the cell surface. Indeed, several other transmembrane proteins, such as the neural cell adhesion molecule (N-CAM) and

the laminin receptor precursor/laminin receptor (LRP/LR), had been reported both to bind to and to mediate PrP^C-dependent signals [34, 66, 101].

An ongoing phage display screening (T.A. Americo, M.H. Magdesian and R. Linden, unpublished) has identified several new candidate PrP^C-binding proteins, of which group I metabotropic glutamate receptors (mGluR1 and mGluR5) were validated as mediators of calcium signals triggered by the interaction of laminin gamma chain with the prion protein [102]. Another PrP^C phage display hit, the α7 nicotinic acetylcholine receptor (α7nAChR), was also shown to mediate calcium signals that follow the interaction of PrP^C with hop/STI1 [103].

The demonstrations of consistent signaling behavior of PrP^C in multiple scenarios reiterate the fundamental question as to how a GPI-anchored protein mediates such context- and cell type-specific signal transfer across the plasma membrane. Molecular interactions involved in varied, PrP^C-mediated signaling events probably differ among distinct cell types because of the availability of the specific binding partners at the surface and extracellular matrix of the various cells. Importantly, although some overlap has been occasionally shown, spatially segregated binding sites may allow the simultaneous interaction of several such ligands with PrP^C [34].

Our concept of the prion protein as a cell surface scaffold protein [34] both follows and extends the current definition of scaffold proteins, which provide physical contact and allosteric interaction of intracellular components of signaling pathways (reviewed in [35, 37]). This hypothesis accounts for both its association with multiple partners, multiple signals and multiple biological responses, as well as with the functional consequences of the presence of PrP^C at the cell surface in the immune system and other organs besides the nervous system. It also predicts that the functional properties of PrP^C depend on the presence of specific PrP^C-binding partners at the cell surface, stoichiometric relationships among PrP^C and its partners, and trafficking of PrP^C relative to all members of putative signaling complexes (Fig. 2).

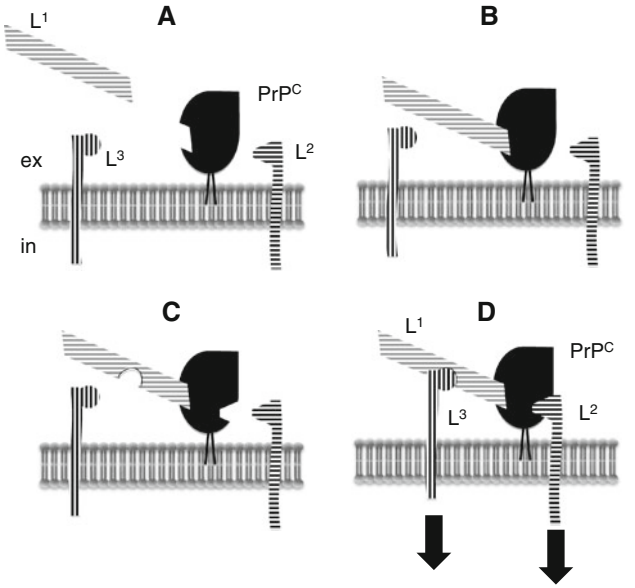

Fig. 2 Recruitment of a PrP^C-mediated signaling complex. The diagram illustrates a model of the recruitment of multicomponent cell surface complexes dependent on the presence of monomeric prion protein. **a** PrP^C is present at the cell surface, together with nearby, non-interacting ligands, which may be either extracellular (ex) molecules (L^1) or membrane proteins (L^2, L^3); **b** primary ligand L^1 binds PrP^C, leading to **c** conformational changes in either PrP^C or L^1, or both; **d** membrane partners of either PrP^C (L^2) or of the primary ligand L^1 (L^3) bind to their partners and transfer signals into the cell (in). Allosteric interactions are required to allow progression from **b** to **c**

Multiple binding partners and allosteric function of the prion protein

High-resolution structural data are available for the prion protein of various species, as determined both by NMR and by protein crystallography, but none in the presence of PrP^C ligands. Instead, only limited information is available concerning the latter's probable binding domains in PrP^C. Their distribution along the entire PrP^C molecule allows for non-competitive binding mechanisms [34], but steric interaction between ligands cannot be ruled out, which might lead to competition even at quite separate regions along the primary structure of PrP^C. Moreover, it is not yet possible to infer the consequences of binding on the conformation of PrP^C, which might result in rearrangement of protein domains.

It follows that many of the hypotheses about the mechanisms and consequences of ligand binding remain speculative, because they rest solely upon the currently available, high-resolution structures of monomeric, isolated PrP^C. Our aim here is, nevertheless, to stimulate an approach to the problem of how PrP^C deals with multiple partners, and the consequences of the dynamic making and breaking of such multicomponent signaling assemblies. The following sections will discuss whether, and to what extent, the concept of the prion protein as a cell surface scaffold protein may fit the hypothesis of allosteric regulation of signal transduction in both physiological and pathophysiological contexts.

Prion protein assembly in the membrane: monomer or homodimer?

The self-assembly of misfolded PrP molecules is a widely accepted model of the infectious scrapie agent [104].

However, the mechanisms of conformational conversion are still poorly defined [105]. Moreover, the supramolecular assembly of the normal prion protein remains elusive.

It has long been assumed that PrP^C is monomeric, based on both physicochemical studies [106–112] as well as NMR structures in solution [38, 39, 73, 113–119]. Notwithstanding, the typical conditions for either physicochemical or NMR studies are usually far from physiological, such as the lack of glycosylation, the use of partial constructs instead of the full-length protein, physical and chemical variables, as well as the absence of physiological interactions with putative binding molecules and cells at close range. Furthermore, membrane anchoring restricts diffusion to a two-dimensional space and ultimately results in the decrease of the dissociation constant of membrane-anchored protein complexes [120, 121].

In contrast, dimerization of native, rather than recombinant, prion protein has been suggested [122], and interactome studies support the hypothesis that normal PrP^C can undergo self-assemby [99, 123]. PrP^C structure has been solved also by protein crystallography, and data are consistent with extensive dimerization interfaces between monomers (Table 1), either from symmetry-related chains or by the swapping of helix 3 between monomers (Fig. 3). These data suggest a possible functional role for such interfaces in the self-assembly of the prion protein into dimers (Table 1), the molecular mechanisms of which await full elucidation. It should be stressed that a dimeric arrangement of the prion protein at the cell surface of normal cells may impart stoichiometric constraints upon signaling complexes scaffolded by PrP^C.

Thus, biophysical data support the potential of PrP^C to form functional self-oligomers regardless of conformational conversion, and an allosteric function may involve both homo-oligomerization and dissociation equilibria in the extracellular microenvironment of the membrane-anchored PrP^C. This may have important physiological consequences, and indeed, evidence for dimerization of the prion protein in trans has been reported, whereby capping of PrP^C induced by antibody cross-linking leads to PrP^C-mediated homophilic cell adhesion required for the stability of adherens cell junctions during embryogenesis, through a mechanism mediated by reggie/flotillin membrane-associated molecules [124].

Copper binding and structural changes of PrP^C

Copper is a well-characterized ligand of the prion protein [125, 126], the functions of which are still unclear, though deemed of major physiological and pathophysiological importance [127–129]. Here we focus on copper-induced modifications of the structure of the prion protein.

Human PrP^C can bind Cu^{2+} at a minimum of five sites, four of which are located in the octarepeat domain at the *N*-terminus and coordinate one Cu^{2+} ion each; an additional Cu^{2+} binding site is composed of His96 and His111, and can bind two copper ions [130, 131]. Interaction with copper reportedly affects the structure and folding stability of the prion protein [132], and Cu^{2+} binding leads to structuring of the *N*-terminal domain [133, 134]. It has been reported that the octarepeat segment $PrP^C_{61–84}$ is well structured in solution in the absence of divalent cations [135], with a conformation similar to the Cu^{2+}-bound complex [127, 136]. Further molecular dynamics simulation of the *N*-terminal domain of human PrP (residues 23–120) loaded with four or five copper ions led to an even more rigid conformation in the octapeptide repeats [134].

Table 1 Crystal structures of the prion protein consistent with dimeric assembly

PDB ID	Description	Buried surface area (Å^2)[a]	Reference
3HAF.pdb–Human $PrP^C_{90–231}$	Monomer in the asymmetric unit, with helix 3 swap between both monomers	6,660	[236]
1I4 M.PDB–Human $PrP^C_{119–226}$	Monomer in the asymmetric unit, with helix 3 swap between both monomers	6,800	[237]
3HJ5.PDB–Human $PrP^C_{90–231}$	Dimer in the asymmetric unit, with helix 3 swap between both monomers	6,310	[236]
3O79.pdb–Rabbit $PrP^C_{127–231}$	Dimer in the asymmetric unit; extensive interaction through H2 and H2-loop-H3; symmetry-related monomers performs only small, local interaction	3,130	[238]
3HER.pdb–Human $PrP^C_{90–231}$	Dimer in the asymmetric unit; subunits disposition in the asymmetric unit reveals supperposition with helix-3 swapped dimers	1,302	[236]
3HEQ.pdb–Human $PrP^C_{90–231}$	Dimer in the asymmetric unit; subunits disposition in the asymmetric unit reveals supperposition with helix-3 swapped dimers	1,102	[236]

[a] Buried surface area was calculated with PISA (http://www.ebi.ac.uk/msd-srv/prot_int/cgi-bin/piserver), based on the assemblies shown in Fig. 3

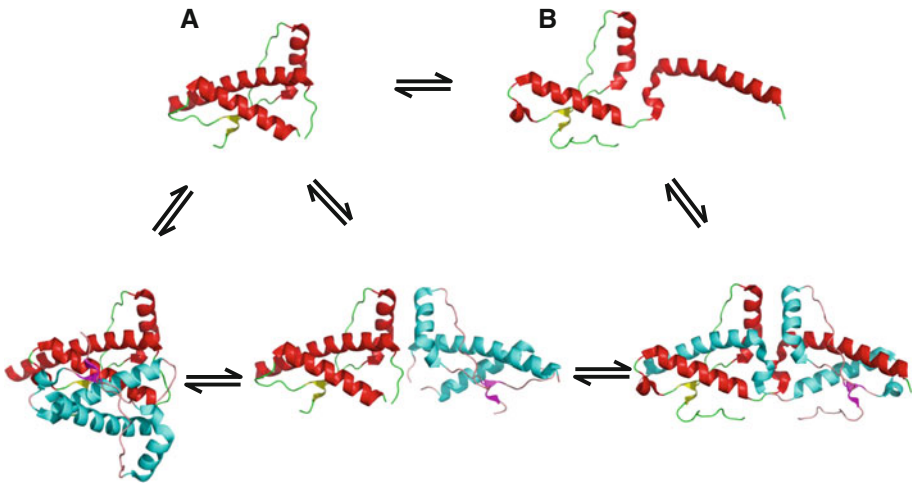

Fig. 3 Schematic diagram of the interchange between PrP^C monomers and dimers. The diagram is based on PrP^C crystal structures and shows hypothetical conformational transitions among two monomeric forms (A for 3HEQ.pdb and B for 1I4 M.pdb) and three possible dimers, as derived from their crystal structures. In addition to the interchain contacts stabilizing such dimers, the association between these monomers would result in the exclusion of surface area to the solvent. The α-helix of each PrP^C monomer is shown in the dimers by *red* or *cyan* colors

This suggests that, depending on the copper/PrP^C molar ratio, the dynamics of PrP is changed, which may alter the availability of the *N*-terminal domain to other ligands.

Recent studies of full-length recombinant PrP (rPrP) showed that copper binding induces both novel interactions between the flexible *N*-terminal and globular *C*-terminal of PrP^C, as well as a compaction of the prion protein, without signs of aggregation at physiological temperature [137]. These data offer new insights into copper-induced structural transitions of rPrP and suggest that the interaction of PrP^C with ligands recognized by either the domain $PrP^C_{144–147}$ in α-helix 1, as well as by the domain $PrP^C_{174–185}$ in α-helix 2, may be allosterically affected by copper binding.

It has also been suggested that copper binding leads to dissociation of PrP^C from a lipid raft-resident partner, thus initiating the former's journey towards non-raft membrane domains, on its way to endocytosis through clathrin-coated vesicles [138]. In addition, glycosaminoglycans (GAGs) bind PrP^C, and the heparan sulfate-derived, GPI-anchored GAG glypican-1 (Gpc-1) interacts with copper-loaded PrP^C [139, 140]. N2a neuroblastoma cells co-internalize PrP^C and Gpc-1 upon induction by copper, indicating that copper loading of PrP^C may impose on the endocytosis of a distinct GPI-anchored molecule.

In turn, binding of PrP^C to Cu^{2+} may be influenced by the glycosylation pattern of the prion protein. Full-length, non-glycosylated PrP^C from sheep brain bound to IMAC resin loaded with either copper or cobalt ions, with higher efficiency than glycosylated forms [141]. This suggests that the access to the copper-binding sites of PrP^C is controlled by the level of glycosylation of the prion protein. This may also affect other PrP^C-binding partners, either through analogous allosteric effects or through steric hindrance by the relatively bulky sugar moieties attached to the prion protein [142].

The interaction of recombinant PrP with the constitutive chaperone Hsc70 was investigated in the presence of copper ions at differing pH values, using an ELISA-based assay [143]. Binding of native PrP to Hsc70 was the greatest at low pH, thus disclosing an allosteric effect of protonation upon rPrP. At low pH, pre-incubation with Cu^{2+} also increased the binding of Hsc70 to rPrP. Two regions within the PrP^C globular domain were mapped as the main Hsc70-binding sites at acidic pH, thus highlighting the allosteric effect of both Cu^{2+} and protonation. The physiological relevance of this interaction is, however, questionable, because measurements were carried out in vitro, using recombinant, non-glycosylated PrP^C, and the binding of extracellular PrP^C to Hsc70 has not been validated either in vivo or ex vivo. On the other hand, a cytosolyic form of PrP^C, which accumulates abnormally upon proteasome inhibition, often forms aggregates that contain Hsc70 [144]. Such molecular chaperones may, in fact, participate in conformational transitions of PrP or protein-protein interactions that lead to TSEs.

Nucleic acids as molecular partners of the prion protein

Nucleic acids (NA) have long been shown to bind to and lead to aggregation of PrP^C [145]. The prion protein is, however, prone to transient aggregation upon binding to polyanions [146–149]. Thus, binding to NA was initially thought of as non-specific, such as typically found for NA-binding proteins and non-specific DNAs, or even between interacting polycations and polyanions [150]. However, further studies

showed that nucleic acid binding to PrP^C is selective [147], and that both aggregation and its time-dependent reversal are tightly regulated, and depend on ligand stoichiometry [151, 152]. In fact, at certain PrP^C:NA ratios a soluble complex is formed, in which the prion protein features a conformation similar to pure PrP^C [148, 152]. Thus, the binding of membrane-anchored PrP^C to NA at the cell surface may not necessarily prompt amyloid formation, and functional properties of the prion protein may be preserved.

Solution-binding studies in equilibrium, achieved after complete reversal of the transient aggregation induced by NA, indicated that small double-stranded DNA binds to the *C*-terminal domain of PrP^C at a 1:1 ratio, accompanied by structural changes in the *N*-terminal domain [152]. This event is favored by acidification [75], in a condition that produces only minor conformational changes of the *C*-terminal domain of PrP^C [73].

Current data indicate that the binding of NA to either the *N*- or *C*-terminals of PrP^C results in substantial rearrangement of both protein and nucleic acid [147, 148, 151–153]. Although the NA binding domain in PrP^C is still unknown, predictive analysis with dbd-PSSM [154] points to a potential for the $PrP^C_{153–174}$ domain to recognize DNA (A.F. Marques and L.M.T.R. Lima, unpublished results). Interestingly, this domain of PrP^C has a high degree of identity with human DNA polymerases 1CLQ.pdb and 1IG9.pdb, differing only in 4 out of 22 amino acids at a region in close proximity to the active site of the latter enzymes.

Attempts made to identify a PrP^C-binding consensus sequence, with the use of various DNA and RNA aptamers, reported NA:PrP^C binding affinities in the nanomolar concentration range [155], consistent with the typical affinity of regulatory proteins. Moreover, the strict dependence of binding affinity upon both NA sequence and the investigated PrP^C domain is also consistent with the typical behavior of classic NA-binding proteins [156–158]. Possible effects of copper, which induces structural gains in the *N*-terminal domain (see above), upon the interaction of PrP^C with NA remain to be investigated.

Interaction of glycosaminoglycans with the prion protein

Glycosaminoglycans have been implicated in the pathogenesis of prion diseases [159–164]. It was shown that GAGs bind the prion protein both when the latter is anchored at the plasma membrane, as well as in a non-glycosylated form in vitro [165, 166], and it was proposed that GAGs in general interact with PrP^C through its *N*-terminal domain [166, 167].

Interaction of the *N*-terminal of PrP^C with pentosan polysulfate (PPS) led to structuring of the octarepeat domain, exposing a hydrophobic surface composed of aligned tryptophan side chains [168]. Similar to the case of nucleic acids, it remains to be investigated whether copper loading of PrP would affect the binding of GAGs, as well as conformational changes [168].

Conflicting results have been reported of the interaction of heparin and heparan sulfate with PrP^C (reviewed in [164]). Certain studies suggested that these GAGs prevent PrP aggregation and conformational conversion [169, 170]. Other studies, in contrast, reported that GAGs either induce or accelerate the structural conversion implicated in TSEs [161, 162].

Recently, the interaction of recombinant prion protein with low molecular weight heparin was investigated as a function of pH. Several binding sites for heparin had already been located in the *N*-terminal domain of PrP^C (reviewed in [34]), but, surprisingly, at pH 5.0, PrP presented 2 heparin-binding sites, in contrast with the unique site found at pH 7.4 [148]. This result implies that changes in pH significantly affect the structure of the complex formed by PrP^C and GAGs.

As pointed out above, the evidence for pH-dependence of PrP^C:heparin interaction may be otherwise relevant for functional properties of PrP^C along progressively acidic endocytic compartments [171, 172], such as the selective requirement of endocytosis for the activation of MAP kinases after binding of hop/STI1 to PrP^C [91, 92]. It may also be important for putative pH-dependent effects among microdomains with distinct local pH determinants, such as negatively charged oligosaccharides attached to surface glycoproteins, including PrP^C itself [173, 174].

Reciprocal remodeling upon binding of PrP^C and hop/STI-1

Several spectroscopic techniques provided evidence that interaction of PrP^C with the co-chaperone hop/STI1 induces reciprocal conformational changes in both proteins [175]. Thus, the binding of murine, recombinant PrP^C to recombinant hop/STI1 entailed a loss in α-helical secondary structure of PrP^C, at least part of which was located in α-helix 1 ($PrP^C_{143–153}$). This may, for example, affect the interaction of PrP^C with ligands such as LPR and N-CAM, which are transmembrane proteins that bind α-helix 1, and transduce PrP^C-dependent signals [66, 176] (Fig. 4a–c).

In turn, three-dimensional, low-resolution models generated from small angle X-ray scattering (SAXS) measurements demonstrated a compaction of the *C*-terminus of hop/STI1 upon binding (Fig. 4d, e). Such tertiary structural changes may either attract or repel ligands of hop/STI1 proper, thus engaging higher order components of the signaling complex in addition to PrP^C ligands.

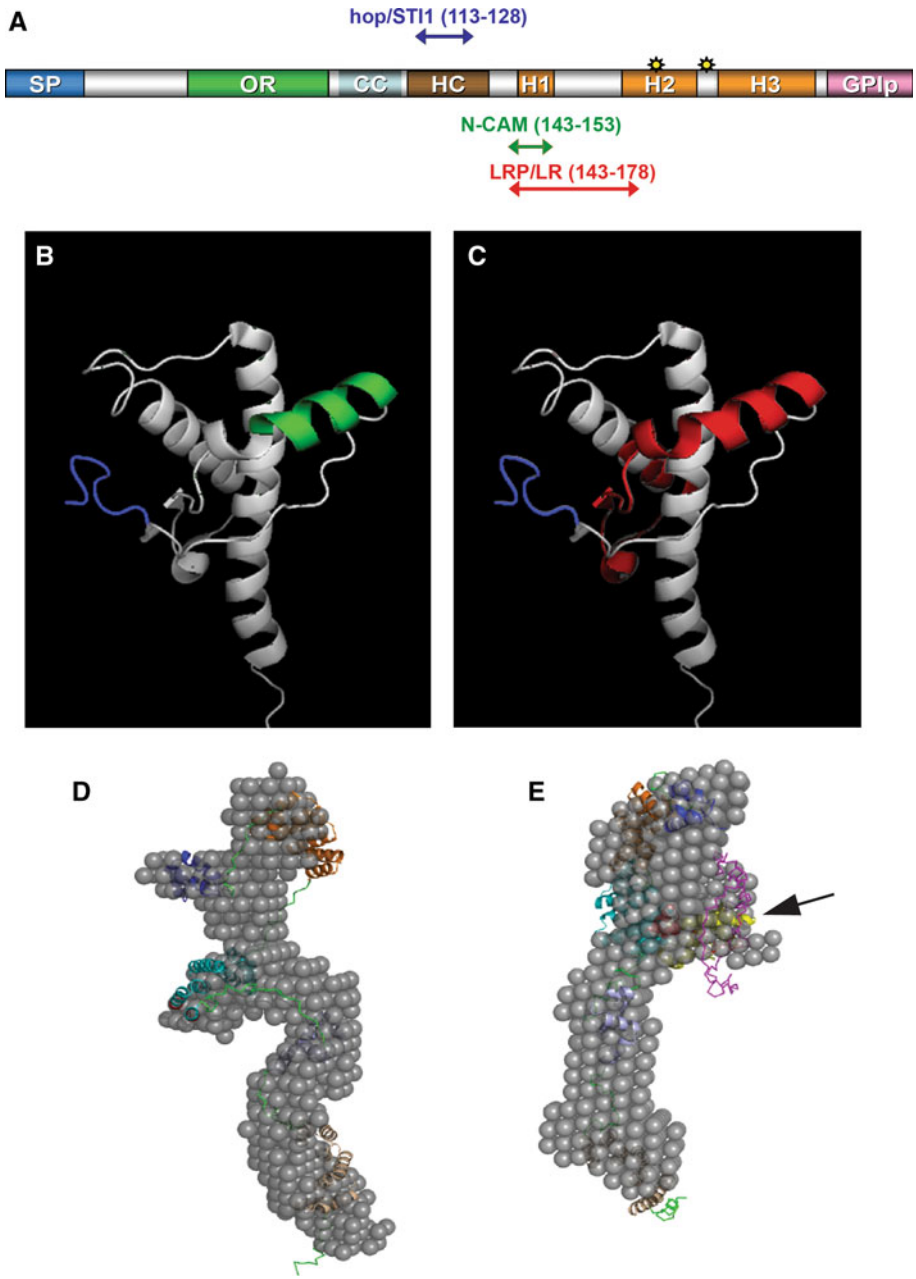

Fig. 4 Reciprocal remodeling of binding partners PrP^C and hop/STI1. **a** Diagram of the prion protein, with indicated domains and sequences of amino acids in mouse PrP^C (SP, signal peptide 1–22; OR, octapeptide repeats 51–91; CC, charged cluster 95–110; HC, hydrophobic core 112–133; H1, H2, H3, α-helices 144–153, 172–194 and 200–224, respectively; GPIp, GPI-anchoring signal 231–254), glycosylation sites (stars 180 and 196), and location of binding domains (*double arrows* with amino acid sequences in parentheses) of hop/STI1 (*blue*), neural cell adhesion molecule (N-CAM, *green*) and the laminin receptor precursor/laminin receptor (LRP/LR, red); **b**, **c** tri-dimensional depiction of the globular domain of PrP^C, highlighting the binding domains indicated in **a** with the same colors; spectrometric techniques unraveled changes in alpha-helix 1 upon binding of $hop/STI1_{230-245}$ to PrP^C. The flexible *N*-terminal tail was omitted for clarity; **d**, **e** low-resolution models (sets of *grey spheres*) of either hop/STI1 alone (**d**), or the hop/STI1:PrP^C complex (**e**), generated from SAXS measurements, reveal a compaction of the tertiary structure of hop/STI1 upon binding to PrP^C (arrow points to PrP^C, where the globular domain is shown in *yellow* and the flexible *N*-terminal tail is shown in *pink*). Modified from [34, 175, 240]

Pertaining to this issue, our data indicated that either the full-length hop/STI1 or a 16 amino acid peptide containing the sequence cognate to PrP^C ($hop/STI1_{230–245}$) induced similar changes in the secondary structure of PrP^C [175]. This may allow either the full ligand hop/STI1 or the peptide alone to engage the same PrP^C ligand(s) and produce the same intracellular signals (Fig. 5). Indeed, in various cell types, either the full-length hop/STI1 or the $hop/STI1_{230–245}$ peptide produced similar PrP^C-dependent neurotrophic effects [89–91, 177] (Fig. 6a), suggesting that signaling was transferred by a PrP^C ligand. As discussed above, one such ligand, detected both by phage display (T.A. Americo et al., unpublished) and validated by biochemical methods may be the α7 nicotinic acetylcholine receptor [103].

Notably, however, whereas full-length hop/STI1 induced proliferation of glioblastoma cells in culture, and deletion of the sequence $hop/STI1_{230–245}$ prevented this effect [178], the $hop/STI1_{230-245}$ peptide alone did not induce glioma cell proliferation (S. Kahn et al., unpublished observations) (Fig. 6b). Accordingly, it was recently shown that hop/STI1 enhanced self-renewal of stem/progenitor cells through its interaction with PrP^C, and, again, the $hop/STI1_{230–245}$ peptide by itself had no effect [179]. A likely explanation for these data is that signaling leading to proliferation of either the glioma or the stem/progenitor

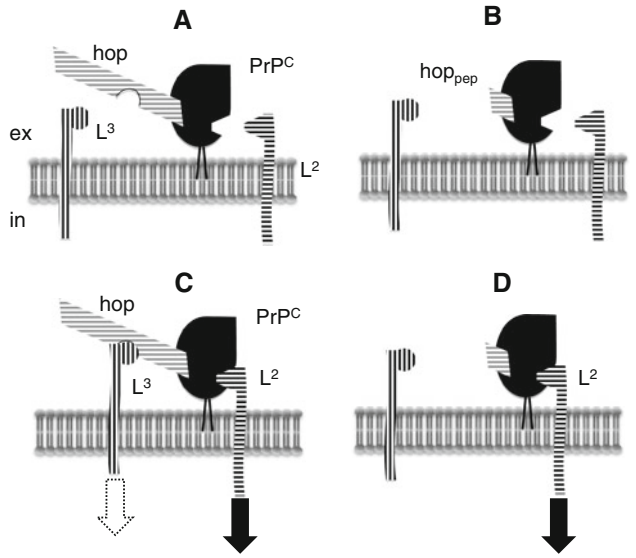

Fig. 5 PrP^C-dependent signaling mediated by similar allosteric effects of either hop/STI1 or the PrP^C-binding peptide hop/$STI1_{230–245}$: the diagrams depict a model of the behavior of PrP^C, when its engagement by either the full-length hop/STI1 (**a**, hop) or only the peptide containing the PrP^C-binding domain (**b**, hop_{pep}) result in the same biological response (**c**, **d**, *black arrow*, see Fig. 6**a**). This scenario probably requires the recruitment of a PrP^C-binding, transmembrane signal transfer molecule (L_2), as a consequence of allosteric effects of hop/STI1 upon PrP^C (see Fig. 4b, c). Engagement of a secondary, hop/STI1-binding transmembrane protein (L_3) may produce additional signals (*dotted arrow*) not required for the current biological response

cells depends on the binding of hop/STI1 to PrP^C, but transmembrane signal transfer requires the recruitment of a hop/STI1 ligand (Fig. 7). An ongoing hop/STI1 phage display screening (M. Magdesian, R. Linden et al., unpublished) has identified several potential candidates for such signal transfer, which are currently under scrutiny.

It should also be noted that extracellular hop/STI1 may induce biological effects irrespective of the presence of the prion protein. Thus, either full-length hop/STI1 or a recombinant protein lacking the PrP^C-binding domain (hop/STI1Δ230–245) equally reduced the proliferation of retinal progenitor cells in either wild-type or PrP^C-null retinas in vitro [180], and a similar result was reported for cultures of brain-derived astrocytes [181]. In addition, antibodies against full-length hop/STI1 prevented cell death of distinct retinal cell types induced by differing means, in either wild-type or PrP^C-null retinas in vitro, whereas antibodies to the PrP^C-binding domain $hop/STI1_{230–245}$ did not [180]. The simplest interpretation for these findings is that hop/STI1 may, by itself, activate transmembrane signal transfer molecules irrespective of PrP^C (Fig. 8a).

However, in neither of the studies above nor, for that matter, in most studies comparing biological effects between wild-type or PrP^C-null cells have kinetic parameters been thoroughly examined. In fact, the conditions in which antibodies to full-length hop/STI1, but not to the PrP^C-binding domain, prevented cell death induced by blockade of protein synthesis [180], were the same in which increased levels of either the full-length hop/STI1 or only of the PrP^C-binding peptide $hop/STI1_{230-245}$ produced a PrP^C-dependent neuroprotective effect [90]. The results, therefore, suggest that the hop/STI1 protein may have PrP^C-dependent, neuroprotective effects, as well as PrP^C-independent, neurodegenerative effects on the same cells. It is possible that transmembrane transfer of either cytodegenerative or cytoprotective signals actually involves the same group of molecules, but the relative concentrations of extracellular hop/STI1, PrP^C, as well as their ligands dictates the final result (Fig. 8b, c). The conflicting signals may either activate distinct downstream pathways or, alternatively, interact due to intracellular networking of multiple signal transfer molecules, conditioned by allosteric effects at the cell surface (Fig. 8c, d).

The overall data are, thus, consistent with biologically relevant, allosteric interaction of PrP^C and hop/STI1, involving ligands of both partners, and fits the concept that PrP^C scaffolds multicomponent, cell surface signaling complexes [34]. Further studies, especially of kinetic parameters and stoichiometric requirements of signal transduction, are warranted to critically test this hypothesis.

Allosteric dysfunction of the prion protein and signal corruption

The preceding sections focused mainly on functional properties of the prion protein, as well as on the effects of certain PrP^C partners upon protein conformation. Although the possibility of loss-of-function components in prion diseases has long been put forward [86, 182, 183], little attention has been directed at the importance of physiological functions of PrP^C in the context of the TSEs. The following discussion will consider hypotheses as to how the scaffold concept, together with allosteric functions of PrP^C, may contribute to the understanding of the pathogenesis of prion disease.

The presentation, course, evolution, histo- and molecular pathology of TSEs are highly variable [184, 185]. Notwithstanding, the prevalent idea is that prion diseases are caused by either a single toxin or by oligomeric toxic species of a defined range of sizes [10]. Although this hypothesis cannot be discarded, it fails to account for the coexistence of three ongoing processes in the course of protein conformation diseases: (1) progressive accretion of monomers to growing oligomers and/or fusion of oligomers; (2) progressive conformational conversion; and (3) their progressive compaction. Most importantly, these events likely occur asynchronously both within and among

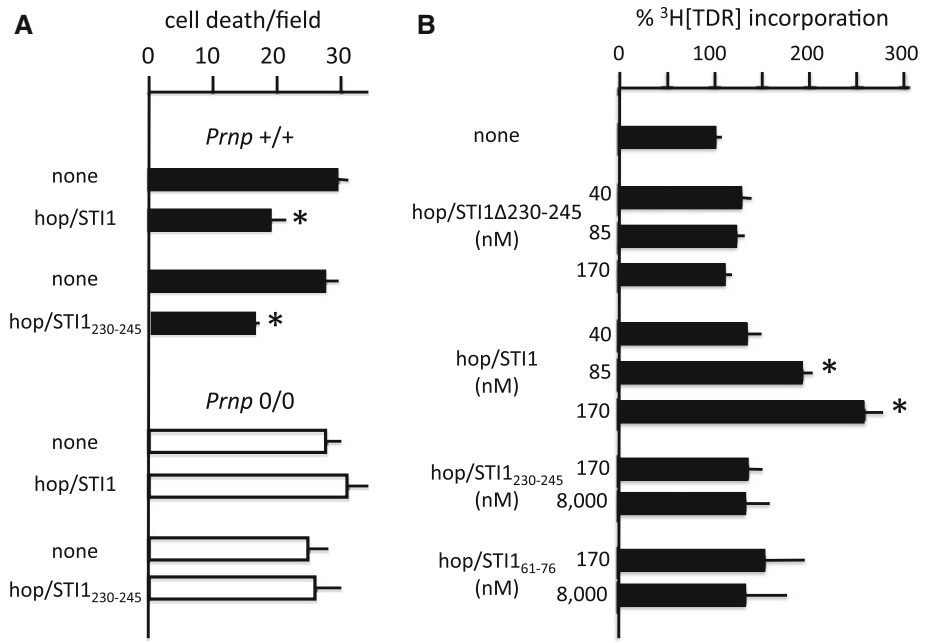

Fig. 6 Comparison of PrP^C-dependent biological effects of hop/STI1 and hop/$STI1_{230–245}$. **a** Neuroprotective effects upon undifferentiated potmitotic cells within the mouse retina. Counts of pyknotic nuclei were done in the ganglion cell layer of retinal explants cultured for 24 h with the inhibitor of protein synthesis anisomycin, either in the absence or the presence of full-length hop/STI1 or the hop/STI1 peptide containing the PrP^C-binding domain (adapted from [90]). Notice the protective effects of both the full-length protein and the PrP^C-binding peptide in wild-type, but not in PrP^C-null nervous tissue. **b** Mitogenic effects on glioblastoma cell cultures. Incorporation of radioactive nucleotide was measured in cultures of the A172 glioblastoma cell line incubated for 24 h with the indicated full-length, truncated proteins or peptides (adapted from [178] and unpublished data). Notice that only the full-length protein induces cell proliferation, whereas no effect was elicited by the PrP^C-binding peptide, by an irrelevant peptide nor by the truncated protein lacking the PrP^C-binding domain

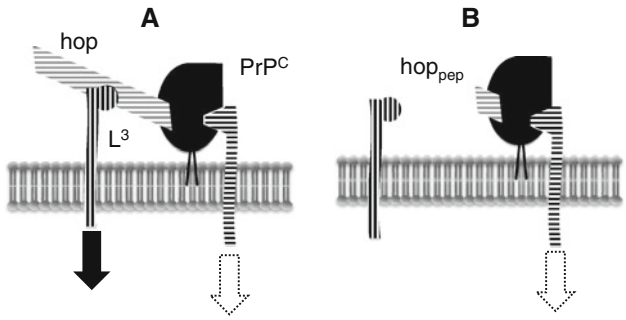

Fig. 7 PrP^C-dependent signaling mediated by a secondary ligand of hop/STI1: **a**, **b** the diagrams depict a model of the events underlying responses induced by hop/STI1, but not by hop/$STI1_{230–245}$ nor by hop/STI1Δ230–245 lacking the PrP^C-binding domain (Fig. 6b). The lack of response to the latter protein indicates that the response (*black arrrow*) depends on PrP^C-hop/STI1 interaction, but the signals produced by the similar allosteric effects of either the full-length or the binding peptide (L_2 and *dotted arrow*) upon PrP^C are innefective to produce the biological response. This scenario probably requires engagement of a productive hop/STI1-binding transmembrane signal transfer molecule (L_3), as a consequence of allosteric effects of PrP^C upon hop/STI1 (see Fig. 4d, e)

distinct areas of the brain, and their coexistence implies that the set of exposed residues of both PrP^C and its anomalous conformer change with time, asynchronously across the affected tissue. This would constantly change the reactivity of the growing aggregates of the prion protein, and their allosteric effects upon the binding and function of physiological or pathophysiological partners in brain tissue.

Notwithstanding the notorious association of anomalous PrP conformers with prion disease, it is still unclear whether or how much conformational conversion is actually required for oligomerization and toxicity. For example, severe overexpression of wild-type PrP^C in mice led to neurological dysfunction accompanied by the finding of no more that 10% of insoluble, mildly protease-resistant aggregates among the whole content of the prion protein at advanced stages of the disease [186]. Unfortunately, that study addressed neither the oligomeric state nor the secondary structure of the protein, albeit the authors have acknowledged the hypothesis that '…high levels of PrP may be toxic in some other way, for example, by saturating or over-stimulating a normal metabolic or signaling pathway activated by PrP^C' [186]. In another study, cross-linking of PrP^C with divalent monoclonal antibodies, but not monovalent Fab fragments, led to neurodegeneration in wild-type mice, with no reported hint of conformational conversion [187]. The latter authors interpreted their

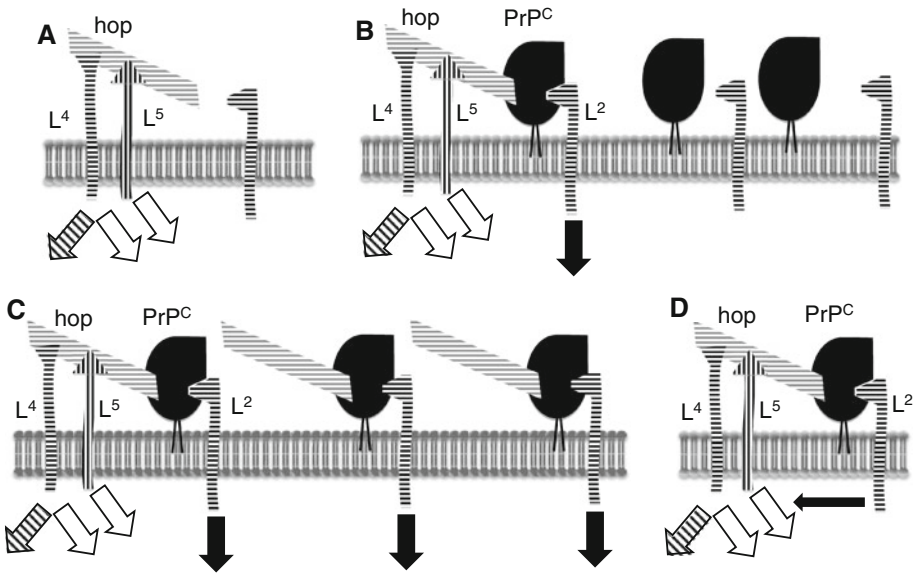

Fig. 8 Hypothetical balance of PrP^C-independent and PrP^C-dependent effects of a PrP^C-binding protein. The diagrams depict the presumptive behavior of the PrP-binding protein hop/STI1 together with various transmembrane signal transduction molecules, in various scenarios. **a** hop/STI1 may bear upon various biological functions, such as cell proliferation and cell death (*hatched* and *white arrows*), independent of PrP^C (see text), and signal transfer may be mediated by either one or more transmembrane molecules; **b**, **c** in certain cases, however, hop/STI1 produces conflicting signals (*white* vs. *black arrows*) via PrP^C-independent and PrP^C-dependent mechanisms, and the resulting biological effect may depend on stoichiometric relationships among the various components of the cell surface signaling modules; **d** alternative events may include intracellular networking of signaling pathways, the net result of which would also depend on the relative amounts of cell surface components

findings as a sign that dimerization of PrP^C led to the toxic events. However, the evidence for natural dimerization of PrP^C (see above) raises the hypothesis that the cross-linking antibodies may have also led to the assembly of higher order oligomers of the prion protein. Finally, recent spectroscopic studies of brain tissue sections have failed to detect anomalous conformers of the prion protein at a stage where both synaptic alterations and behavioral signs are already detectable in a mouse model of infectious prion disease (V.H. Perry, personal communication). It is possible that toxic PrP species that contribute to early pathological events may be too small, diffuse or rare, thus making their detection difficult by the techniques used in the studies mentioned above. Nonetheless, those results are also consistent with an alternative hypothesis that conformational conversion may not be required for PrP^C aggregate-dependent toxicity, at least at early stages of the TSEs.

The dynamics of changes among a heterogeneous population of oligo- and multimers, slack and compact aggregates, with variable content of anomalous conformers, is probably relevant for the heterogeneity and the course of the prion diseases. Still, both the time and the asynchrony factors are often ignored in the interpretation of experimental data of TSEs, as well as in other neurodegenerative disorders. In contrast, recent work raised the hypothesis that the pathogenesis of Alzheimer's disease may actually be linked to the dynamic events of incorporation of β-amyloid monomers into growing protofibrils rather than to a specific class of oligomers [188]. Analogous events involving the prion protein may be relevant to the TSEs as well, and deserve thorough investigation.

It is, thus, questionable that a defined toxic molecular species, at a specific time, is responsible for the complex cellular events that underlie the pathogenesis of TSEs. Misfolded and aggregated anomalous conformers of the prion protein may, by themselves, have toxic gain-of-function properties. Even so, disturbances of the scaffold and allosteric functions of PrP^C probably add to the effects of such toxic species, or, alternatively, are responsible for specific pathogenic events. A likely scenario is that, in the course of prion diseases, the brain progresses toward neurodegeneration from a framework of physiological functions of normal PrP^C, through either several stages or a continuum of corrupted cellular signals, leading to pathological events, such as the early changes of synapse morphology and function, followed by progressive neuron death [189–191]. It follows that the nature of the molecular interactions of PrP^C and their disruption at the earliest stages of the TSEs is pivotal for the understanding of homeostatic corruption associated with prion diseases.

It is particularly noteworthy that the GPI-anchoring of the prion protein to the membrane seems to be required for the full-blown disease in vivo, though not for the

accumulation of the pathognomonic compact, protease-resistant aggregates, nor for infectious transmission [82, 83]. These data further highlight the importance of the interactions of PrP^C with cell surface and transmembrane molecules, the ensuing allosteric effects, as well as their consequences for signal transduction. The scaffold hypothesis predicts that, in the course of TSEs, the assembly of cell surface signaling complexes organized by the prion protein, together with their downstream effects, change along with progressive oligomerization, conformational conversion and compaction of the aggregates. Such signal corruption may include either the gain or the loss of specific signals associated with PrP^C partners [192], as well as effects upon signaling kinetics due to the derangement of multicomponent complexes scaffolded by PrP^C [34, 193], both of which are likely to occur upon either the masking or the exposure of specific domains of the prion protein.

Multiple effects can be expected from oligomerization, cross-linking or merely an increased content of the GPI-anchored prion protein. Events may include the disassembly of signaling modules, due to disruption of stoichiometric relationships between PrP^C and its partners (Fig. 9a). In fact, the possible interplay of monomers and dimers of PrP^C (see above) should also be taken into account to understand the physiological framework of PrP^C-mediated signaling, while the accruing of each monomer (or dimer) to a growing oligomer would further disrupt local stoichiometry of cell surface signaling complexes.

This, as well as further accretion of monomers, is expected to exact either physiological or pathological oligomerization of PrP^C-binding signal transducers, such as membrane receptors (Fig. 9b). Thus, in cells bearing oligomers of PrP^C at their surface and/or internal membranes, abnormal homo- or hetero-oligomerization of receptors may robustly affect ligand affinity, kinetics of signal transduction and receptor trafficking [194–198]. In addition, oligomerization imparts changes in short-term, lateral diffusion at the plasma membrane [199, 200], with likely consequences upon both the kinetics of recycling of the cell surface PrP^C, as well as of PrP^C-mediated signaling.

The previous events, plus further multimerization and compaction, tend to progressively favor steric hindrance [201–204], eventually blocking the assembly of cell surface signaling modules (Fig. 9c). Notably, several studies suggest that, in various neurodegenerative diseases, the pathognomonic aggregates detectable at light microscopical examination may actually offer neuroprotection [205–210], probably because steric hindrance prevents any productive association of the compact aggregates with molecular partners required for neurotoxic signaling.

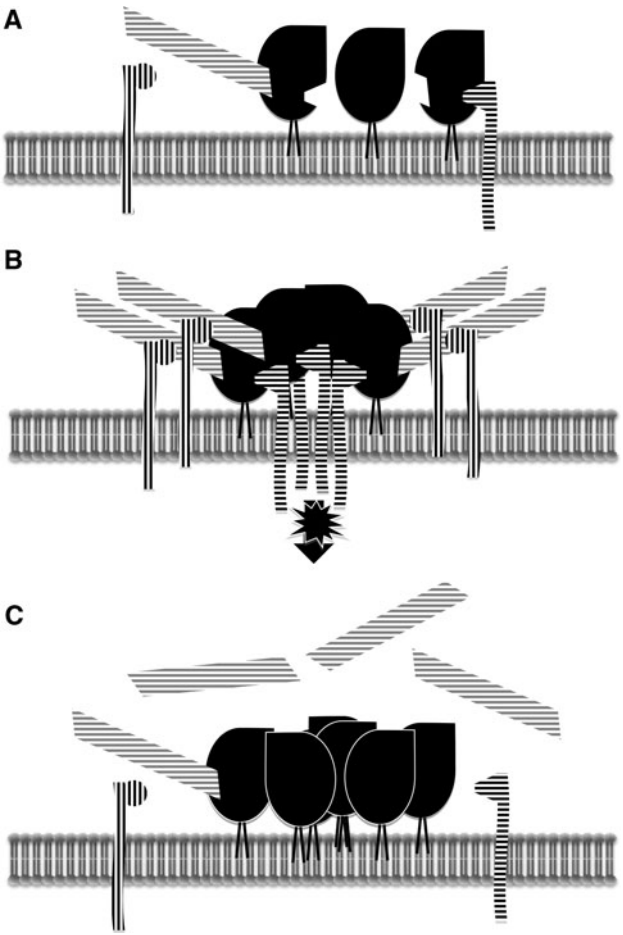

Fig. 9 Multiple events of signal corruption expected from oligomerization and progressive compaction of aggregates of the prion protein. **a** Initial events may disrupt stoichiometrical relationships between PrP^C and nearby ligands, leading to disassembly of cell surface signaling modules; **b** further oligo- and multimerization may lead to abnormal oligomerization of PrP^C ligands, such as membrane receptors, with ensuing corruption of signal transduction through such receptors; **c** further compaction of aggregates of the prion protein favors steric hindrance, thus preventing binding of PrP^C ligands and the assembly of cell surface signaling modules

It should be noted that separation of these three categories of effects serves only to highlight individual components of a complex, dynamic scenario of signal derangement. Simultaneously, combined with the effects predicted from simple oligomerization, the conformational conversion would add to both the propensity of protein aggregation [211, 212] and to changes in ligand binding, which are expected to follow modification of the secondary structure of the protein (Fig. 10).

The progressive, asynchronous occurrence of these dynamic events in any given neuronal population most likely spreads, also asynchronously, along the interconnections of brain areas and nuclei, therefore adding to both the pathogenesis of the diseases, as well as to the production of specific signs and symptoms.

It has recently been demonstrated that the prion protein specifically binds β-amyloid (Aβ) oligomers [213], although the significance of such binding for Alzheimer's disease is still under debate [214–223]. Nonetheless, it was reported that Aβ disturbs the trafficking of the prion protein, leading to an accumulation of PrP^C at the cell surface [224], and that both Aβ and monoclonal antibodies cross-link PrP^C, to which synaptic toxicity was attributed [225]. As discussed above, the accumulation and cross-linking of PrP^C are both likely relevant for cell signaling (Fig. 9), and the scaffold hypothesis may explain, for example, why an increasing number of differing membrane receptors have been implicated in toxic signaling induced by various β-amyloid aggregates [226–232] (Fig. 10).

Data have also been reported of possible interference of the prion protein in other neurological diseases, such as primary progressive aphasia [233], or in experimental models of amyotrophic lateral sclerosis [234, 235]. It should also be pointed out that changes in the stoichiometry of the components of PrP^C-scaffolded signaling modules may be relevant not only for the nervous system, but also for other cell types and tissues, such as muscle and the immune system [34]. An intriguing possibility is that disturbance of the scaffold and allosteric functions of the prion protein may be also involved in the pathogenesis of a variety of diseases other than the TSEs.

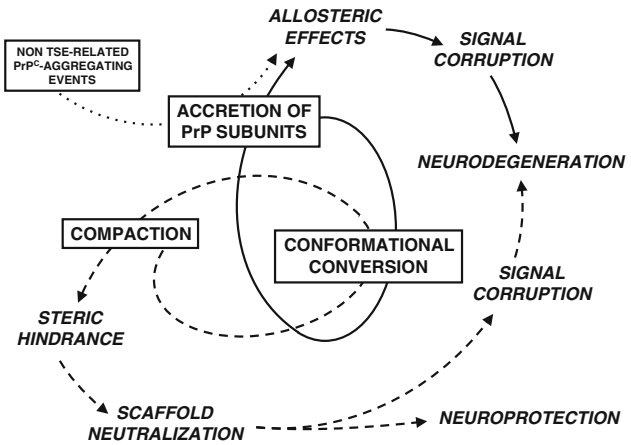

Fig. 10 Diagram of proposed pathogenic events due to dysfunction of the scaffold properties of the prion protein. The figure depicts how the asynchronous accretion of monomeric or dimeric PrP^C to growing oligomers, conformational conversion of an unknown proportion of the protein molecules within agregates and progressive compaction of the aggregates may lead to the pathogenesis of TSE and other neurodegenerations. The cycle of accretion of monomers together with conformational conversion is thought to heavily impose upon the properties of PrP^C-scaffolded signaling modules, leading to allosteric effects and ensuing signal corruption, which may result in neurodegeneration (*arrows*). Conformational conversion is, in turn, expected to fuel progressive aggregation and compaction, leading to steric hindrance, which may either cause further signal corruption and neurodegeneration, or, at late stages, contribute to protect the tissue from the recurring cycles of monomer accretion and dynamically changing allosteric effects (*dashed arrows*). Signal corruption due to accretion of PrP^C subunits may also be triggered by non TSE-related aggregation events, such as cross-linking by Aβ oligomers (*dotted line*)

Conclusion and perspectives

The preceding sections discussed structural constraints involved in the interaction of the prion protein with various binding molecules. The latter include proteins, such as hop/STI1, nucleic acids and glycosaminoglycans, and extend to the effects of pH. Possible instances of allosteric control were discussed, associated with changes in the interaction of PrP^C with a third partner.

Analysis of structural changes due to the interaction of the prion protein with its multiple partners is still precarious, and little data have so far been gathered as to the functional properties of molecular complexes scaffolded by the prion protein. For most putative ligands of PrP^C, no structural data relevant to their binding have been published so far. Therefore, this review serves basically to set a framework for future studies. Notwithstanding, the available data higlight the importance of understanding the allosteric function and dysfunction of the prion protein.

One important caveat is that most structural data gathered to date refer to the isolated prion protein in artificial conditions, which may differ substantially from the environment where PrP^C resides in living cells. Efforts are warranted to try and reach conditions as close as possible to those prevailing in physiological microenvironments, such as the cell surface, endocytic vesicles involved in the trafficking of PrP^C and also the Golgi, where nascent PrP^C molecules may interact with either nascent or resident partners. In addition, the events that occur upon the binding of PrP^C with multiple partners must be identified to help understand the role of PrP^C in cell signaling both in the nervous system as well as in other cell types containing substantial amounts of PrP^C.

The scaffold hypothesis further raises key questions regarding the composition of PrP^C oligomers. There is pressing need to clarify the components and the kinetics of growth of PrP oligomers in early stages of TSEs, inclusive of the relative contributions of either normal or anomalous conformers, to understand the nature of the cellular signals associated with these deadly diseases.

In conclusion, both the understanding of the pathogenesis of TSEs and the development of their effective treatment, and perhaps the management of other diseases, such as Alzheimer's disease, where both protein oligomers and the prion protein may play a role, require a change in paradigm, where instead of targeting an elusive toxic species, one should aim at the understanding of the kinetic

behavior of rapidly changing oligo- and multimers, together with the allosteric effects associated with the making and breaking of signaling complexes that lead to the dynamic signal corruption at the root of pathogenic events due to dysfunction of the prion protein.

Acknowledgments The authors' work is supported by grants from CNPq, FAPERJ, and the National Institute of Structural Biology and Bioimaging (INBEB-MCT).

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