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FUNCTIONS OF THE PRION PROTEIN

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Abstract

Although initially disregarded compared to prion pathogenesis, the functions exerted by the cellular prion protein PrP^C have gained much interest over the past two decades. Research aiming at unravelling PrP^C functions started to intensify when it became appreciated that it would give clues as to how it is subverted in the context of prion infection, and more recently, in the context of Alzheimer's disease. It must now be admitted that PrP^C is implicated in an incredible variety of biological processes, including neuronal homeostasis, stem cell fate, protection against stress, or cell adhesion. It appears that these diverse roles can all be fulfilled through the involvement of PrP^C in cell signalling events. Our aim here is to provide an overview of our current understanding of PrP^C functions from the animal to the molecular scale and to highlight some of the remaining gaps that should be addressed in future research.

Keywords: CNS function, cell fate and differentiation, protection against stress, cell adhesion, cell signalling

1. Introduction

Historically, the cellular prion protein PrP^C was discovered as the normal host counterpart of the pathogenic scrapie prion protein (PrP^{Sc}), itself the main component of the infectious agent responsible for Transmissible Spongiform Encephalopathies ¹. In the early years of prion research, unravelling PrP^C normal function seemed not as much a priority as grasping the properties of PrP^{Sc} and understanding TSE-associated pathogenesis. This view was reversed when it came to light that unravelling PrP^C function would illuminate how it is corrupted by pathogenic prions to promote neurodegeneration. The first generation of PrP-knockout mice in the early 90's ² set the

stage for studying PrP^C physiological role. Although somehow disappointing at first glance since these mice develop with no overt phenotype, they have actually allowed bringing to light subtle defects and remain a major tool to dissect PrP^C function. At the molecular scale, much insight has been gained through the identification of PrP^C-interacting molecules, as well as PrP^C-dependent signalling events. In addition, in more recent years, our view of PrP^C has evolved from a protein majorly involved in neuronal function to a broad player in cellular homeostasis, in various tissues and at various stages of life. Another equally important concept that has emerged is that PrP^C exerts a broad protective role against various types of stresses, which has notably been exemplified upon challenging PrP-null animals. In this chapter, we will address these different points with the aim to provide a comprehensive view of our current knowledge of PrP^C functions.

2. The basics of PrP^C

2.1. PrP^C from gene to function

PrP^C is encoded by a single gene denoted *Prnp*, which is located on chromosome 20 in man and 2 in mouse. It possesses two paralogues, *Prnd* and *Sprn*, encoding the Doppel and Shadoo proteins respectively, whose properties have been reviewed recently ³ and will not be discussed further in the present chapter. According to species, the *Prnp* gene contains 2 or 3 exons, the entire coding region being contained in the last exon, excluding the possibility of alternative splicing ⁴. The resulting native protein of 253 amino acids (human numbering) is processed to generate a mature form of 208 residues lacking its N-terminal-most signal peptide and modified in its C-terminus with the attachment of a glycosyl-phosphatidyl (GPI) moiety allowing for its anchoring to the extracellular plasma membrane ⁵. Two topological transmembrane variants with either

their N-terminus (CtmPrP) or C-terminus (NtmPrP) portions in the cytosol have been described ⁶, and may account for the interaction of PrP^C with several cytosolic partners. In terms of secondary/tertiary structure, it can be globally divided into a N-terminally intrinsically disordered domain – often referred to as “flexible tail”-, a central hydrophobic domain and a C-terminal globular domain (Fig. 1). The latter region contains two Asparagine residues that can be N-glycosylated, flanked by two Cysteine residues forming a disulfide bridge. In addition to the full-length isoforms, PrP^C can undergo proteolytic processing at various positions ⁷. The best characterized and most conserved cleavage site lies in the central domain (alpha-cleavage site) and leads to the production of the N1 soluble fragment and the GPI-anchored C1 fragment (Fig. 1). Finally, PrP^C may exist under soluble full-length isoforms, resulting either from a phospholipase-dependent GPI cleavage or from proteolytic cleavage at residues 228/229 ^{7,8}. Thus, the various post-translational modifications that can impact on PrP^C give rise to a plethora of isoforms, which add to the complexity when studying PrP^C function.

From an evolutionary perspective, it is noteworthy that the structural features of PrP^C are conserved in vertebrates ⁹, most notably in mammals ¹⁰, underscoring their functional importance. Interestingly, bioinformatics analyses suggest that the *Prnp* gene family may originate from a common ancestor of the ZIP family of metal ion transporter ¹¹. In this scheme, the metal binding capacity of PrP^C (see below) would represent one of its ancestral functions.

2.2. PrP^C expression and localization

Delineating the functions of PrP^C necessitates taking into account when and where it is expressed. During embryonic development, *Prnp* mRNA expression was reported to start around embryonic day 6.5 (E6.5) in extra-embryonic tissues ¹², followed by the

cardiac mesoderm at E7.5 ¹³ and the developing CNS at E8 ¹⁴. Around E9, PrP^C is detected in the developing nervous and cardiovascular systems as well as in extra-embryonic regions ¹⁵, in line with its role in stem cell self-renewal (see below). The observation that PrP^C expression in extra embryonic annexes is maintained at early differentiation stages fits in with an important - albeit little explored- role for this protein in the physiology of the placenta (reviewed in ¹⁶) and in angiogenesis ^{17,18}.

During neurodevelopment, PrP^C remains abundant in sites of active neurogenesis such as the ventricular zone, while it is also highly expressed in regions where maturing neurons migrate such as the hippocampus and the thalamic and hypothalamic regions, consistent with its involvement in neuronal differentiation ¹⁹. Analysis of PrP^C expression during forebrain development in human also indicates that synapses exhibit increasing amounts of PrP^C throughout synaptogenesis ²⁰. In the adult, while PrP^C still is enriched in the brain not only in neurons but also in glia and endothelial cells of the blood brain barrier ²¹, it is also widely expressed in all tissues.

At the sub-cellular scale, most PrP^C is found at the membrane, and is notably enriched in lipid rafts, or at the synapse in neurons ^{22,23}. This plasma membrane location led to the assumption that it may act as a cell surface receptor or co-receptor and instruct signal transduction events. PrP^C-dependent signalling now represents one of the most fertile areas of research related to PrP^C function, and will be addressed in detail in section 8.

Beyond the membrane, a less studied spatial location is the cytosol, where PrP^C seems to accumulate in conditions of stress ²⁴. Other locations include the base of the primary cilium ¹⁵, the nucleus ²⁵ or extracellular vesicles such as exosomes ²⁶. At present, the mechanisms sustaining the trafficking of PrP^C to the cilia or its shuttling to the nucleus remain enigmatic.

3. Lessons from knockout models

In the early 90's, several groups reported on the generation of PrP-null mice. Beyond a drastic neurodegenerating phenotype due to the accidental upregulation of the PrP paralogue Doppel, whose gene is located downstream from *Prnp*²⁷ and a mis-attributed regulation of phagocytosis due to confounding effects of the flanking gene *Sirpa*²⁸, these various models have revealed that PrP^C deficiency is associated with a variety of neurological defects. These include alterations in memory and locomotor activity²⁹, circadian rhythms^{30,31}, olfaction³², pain sensitivity^{31,33}, and a depressive-like behaviour³⁴. Interestingly, some defects appear to worsen with age³⁵, suggesting that the lack of PrP^C may be more detrimental at defined periods of life³⁶. *Prnp*-null mice have also been instrumental in revealing that PrP^C is necessary for the long-term maintenance of hematopoietic stem cells (HSCs)³⁷ and for the proliferation of neural progenitors³⁸, opening the question of the role exerted by this protein in stem cell biology (see below and³⁹). Another set of observations has exemplified an increased vulnerability of PrP-null mice to various types of stresses: ischemia⁴⁰, behavioural stresses⁴¹ or inflammatory conditions (reviewed in⁴²). Perhaps the best understood phenotype at present is the demyelinating disease not only observed in first-generation PrP knockout mice⁴³ but also confirmed in *Prnp*-ablated mice generated through genome editing⁴⁴. Indeed, molecular studies have shown that the PrP^C N-terminal acts as an agonistic ligand of the Adgrg6 receptor, whose activation is necessary for myelin maintenance⁴⁵. Finally, in contrast to the mild phenotypes observed in mice invalidated for PrP^C, a drastic impact of the knockdown of the fish *Prnp* orthologue *PrP-1* was reported in zebrafish, with a lethal phenotype due to cell adhesion and gastrulation defects⁴⁶. Interestingly, the phenotype of *PrP-1* morphants could be rescued using mouse PrP^C, highlighting an evolutionary conserved function⁴⁶. Readers are referred to the recent

review by Halliez et al. for a comprehensive view of the consequences of PrP^C invalidation ⁴⁷.

4. Miscellaneous roles in CNS function

4.1. Cognitive and behavioural functions

Because TSE are neurodegenerative diseases and because PrP^C is most abundantly expressed in the brain, PrP^C function has been the most studied in the context of neurons. The notion that pathogenic prions exert their toxicity by deviating the normal function of PrP^C in neurons ⁴⁸ has further boosted research on the physiological role exerted by PrP^C in these cells. As mentioned above, synaptic deficits were among the first defects to be described in PrP-null mice ⁴⁹, although initially questioned ⁵⁰. Further studies have consistently reported on alterations of synaptic activity in absence of PrP^C ^{51,52}, including in the context where PrP^C is ablated at a post-natal stage ⁵³. Incidentally, the notion that PrP^C may contribute to memory is also indirectly supported by the identification of SNPs in the human *PRNP* gene associated with enhanced long-term memory ⁵⁴ and the demonstration that *PRNP* is a target gene of FOXP2, a key transcription factor involved in language development ⁵⁵. The regulation of *Prnp* gene expression by the E4BP4 transcription factor ⁵⁶, which is involved in the regulation of the circadian clock ⁵⁷, may on another hand accommodate the link between PrP^C and circadian rhythms ^{30,31} and contribute to the induction of PrP^C mRNAs in response to melatonin ⁵⁸.

4.2. Neuritogenesis and neuronal differentiation

From a mechanistic point of view, the contribution of PrP^C to synaptic function may operate at different levels. A first axis relates to neuronal differentiation and brain wiring. The contribution of PrP^C to neuronal differentiation has been mostly

investigated from a cell architecture point of view, although the implementation of neuronal polarity and that of neurotransmitter-associated functions are intimately connected ⁵⁹, and are both altered in the context of prion infection ⁶⁰. Several studies indeed have exemplified a participation of PrP^C to neurite elongation and synapse development ⁶¹⁻⁶⁶. This positive action of PrP^C on neuritogenesis may depend on the functional interaction of PrP^C with various partners: the neural cell adhesion molecule NCAM ^{61,66}, laminin ^{63,67}, STI1 ^{68,69}, integrins ^{65,70,71}, vitronectin ⁷⁰ or itself ⁶¹ and the recruitment of signal transduction cascades, as will be described below. On another hand, PrP^C was shown to potentiate the inhibitory effect of the contactin-associated protein (Caspr) on neurite outgrowth in a Reelin-dependent manner ⁷². In mature neurons, PrP^C may further contribute to the structural maintenance of the synapse by regulating cytoskeletal components such as cofilin or local protein translation, two processes that are impaired under prion infection ^{60,73}.

4.3. Balancing neuroprotection and neurotoxicity

Given the beneficial functions exerted by PrP^C in neuronal physiology (see also section 6 for the protective role of PrP^C against stress), it came as a surprise that antibody-mediated crosslinking of PrP^C caused extensive neuronal apoptosis *in vivo* ⁷⁴, hinting at a pro-apoptotic role of this protein. Several observations obtained in mice expressing mutant forms of PrP^C have additionally brought insight into the dichotomous role of PrP^C as a trigger of pro-survival or pro-apoptotic cascades in neurons. For instance, mice expressing a N-terminally truncated form of PrP^C (Δ 32-121 or Δ 32-134) were shown to suffer from ataxia and cerebellar degeneration ⁷⁵, pointing to a protective role of the N-terminal flexible tail of PrP^C. Deletions of the central hydrophobic region (Δ 94-134 or Δ 105-125) also caused drastic spontaneous cerebellar disorders ^{76,77}. Deleting the central domain in PrP^C notably obliterates the alpha-cleavage site and precludes the

generation of the soluble N1 fragment, raising the possibility that these severe phenotypes are caused – at least partly - by the lack of N1.

More recently, several elegant studies lead by the Aguzzi's group and exploiting a panel of antibodies targeting various epitopes of PrP^C have shed further light on the respective roles of the N-terminal and C-terminal regions of PrP^C. One outstanding conclusion of these works is that antibodies targeting the globular domain exert a neurotoxic effect in mice or cerebellar organotypic slices and seem to mimic the effect of prion infection ⁷⁸, while those directed against the flexible tail are innocuous ⁷⁹. Of note, the latter protect against the deleterious effects of antibodies to the globular domain ⁷⁸, as well as against the toxicity of PrP^C mutants bearing a deletion of the central domain (PrP^Δ94-134) ⁷⁹. These observations hence corroborate the notion that the flexible tail of PrP^C and its globular domain exert distinct action. Since the flexible tail of PrP^C was recently identified as an agonistic ligand of the Adgrg6 receptor to sustain myelin maintenance ⁴⁵, we may envision that it exerts broader agonistic effects on yet-to-be-identified receptor(s) to maintain brain homeostasis. Other members of the adhesion GPCR family beyond Adgrg6 itself clearly represent candidates for relaying the protective action of PrP^C N-terminal tail in view of their conspicuous roles in nervous system development and function ⁸⁰.

4.4. Beyond neurons: PrP^C in glia

It has recently emerged that neural circuits are also shaped by complex neuron-glia interactions ^{81,82}. In this scheme, the contribution of PrP^C to proper brain function may involve dialogues between neurons and other cell types, as described for the PrP^C-Adgrg6 duo at the interface between neurons and Schwann cells ⁴⁵. For instance, PrP^C from astrocytes was shown to promote neuritogenesis and neuronal survival ⁸³. More generally, PrP^C from astrocytes appears to play a protective role under stress conditions,

both on astrocytes themselves ⁸⁴, but also on neighbouring neurons ⁸⁵. In the latter study, PrP^C was shown to be transferred from astrocytes to neurons via exosomes ⁸⁵. Adding yet another layer of complexity to the picture, PrP^C appears to regulate the secretion of exosomes itself ⁸⁶. We may hence suspect that the absence of PrP^C may have broader impact on brain extracellular vesicles, which represents an important means of intercellular communication ⁸⁷. Other consequences of PrP deficiency in astrocytes include defects in lactate transport ⁸⁸, as well as altered excitatory amino acid transporter activity ^{89,90}.

4.5. The metal connection

The involvement of PrP^C in neuronal functions may further arise from its ability to bind divalent cations in its N-terminal region. Following the first report that PrP^C binds copper *in vivo* ⁹¹, several studies have suggested that PrP^C may be involved in the regulation of copper concentration at the synapse (see ⁹² for review). Interestingly, copper appears to influence some PrP^C-mediated cell signalling events ^{93,94}. More recently, Gasperini et al found that PrP^C cooperates with copper to induce S-nitrosylation of the NMDA receptor ⁹⁵. Beyond copper, PrP^C also binds zinc ions and facilitate their uptake in neuronal cells via AMPA receptors ⁹⁶. Altogether, several reports converge onto a protective role against glutamate or AMPA/kainate-induced excitotoxicity ^{95,97-99}. It is noteworthy that this protective role with respect to neuron excitability is conserved in fish ¹⁰⁰.

4.6. From neurotransmitter receptors to neurotransmitter-associated functions

The above studies further point to crosstalks between PrP^C and neurotransmitter receptors. These functional interactions, which have been reviewed recently ¹⁰¹, extend beyond NMDA and AMPA receptors and also include serotonergic ^{94,102,103} or cholinergic ^{104,105} receptors. An interaction between PrP^C and the purinergic P2X4R has also been

recently described ¹⁰⁶. A related emerging theme is the broader implication of PrP^C in the fine-tuning of neurotransmitter-associated functions. Indeed, at the animal scale, the absence of PrP^C appears to induce defects in the dopaminergic ^{107,108}, cholinergic ¹⁰⁹ or serotonergic ^{31,107} systems. As for the latter, PrP^C contributes to the regulation of monoamine synthesis ¹¹⁰, catabolism ¹¹¹, or release ⁹⁴ through various cell-signalling dependent mechanisms. Interestingly, a modulatory role of PrP^C on synaptic release was recently exemplified at the *Drosophila* neuro-muscular junction ¹¹², further adding support to a potentiating role of PrP^C in synaptic transmission ¹¹³ (for review).

5. Cell fate and differentiation

5.1. Stem cell self-renewal and expansion

Interest for a potential contribution of PrP^C to the biology of stem cells arose with the discovery that it is abundantly expressed in HSCs, including the most immature Lin⁻Sca⁺Endoglin⁺ subpopulation, and that it is necessary for the long-term maintenance of these cells ³⁷. PrP^C was subsequently shown to be highly expressed in neural ³⁸, cardiac ¹³, mammary ¹¹⁴, skeletal muscle ¹¹⁵ or mesenchymal ¹¹⁶ progenitors. Thus, high PrP^C expression appears as a generic feature of various types of stem cells. In line with this, PrP^C was shown to be upregulated following the induction of multipotential embryonic stem (ES) or carcinoma (EC) cells towards a more restricted neural ^{117,118} or cardiac ¹³ fate, or during their spontaneous differentiation ^{119,120}. Furthermore, expressing PrP^C in ES cells grown under self-renewal conditions was reported to promote their induction towards lineages of the three germ layers ¹²¹. Altogether, these observations posit PrP^C as an important player in stem cell fate determination and raise the question as to the cellular processes to which it may participate in a stem cell context. One recurring theme is its contribution to proliferation. For instance, PrP^C levels correlate with the

proliferation rate of neural progenitors in two neurogenic regions in adult mice: the subventricular zone (SVZ) and the dentate gyrus (DG) ³⁸. *Ex vivo*, neurospheres from fetal ¹²² or adult ¹²³ brain further proliferate less efficiently when derived from *Prnp* knockout versus wild type mice. These defects may notably be explained by a lack of response to the PrP^C ligand STI1 ¹²². The contribution of PrP^C to stem cell proliferation also holds true for mesenchymal progenitors ¹¹⁶. Interestingly, PrP^C expression was recently shown to be induced after hypoxia preconditioning and to enhance the survival and proliferation of transplanted mesenchymal stem cells (MSCs) ¹²⁴. That PrP^C may strengthen tissue repair was also exemplified in the context of HSC transplantation ³⁷ or muscle regeneration ¹¹⁵. Another notable example is the participation of PrP^C to recovery from ischemia ^{18,40,125,126}, possibly after mobilization by its ligand STI1 ¹²⁷. Finally, because PrP^C remains highly expressed in adult neurogenic zones, it is likely to take part to brain repair following stress or injury, a process that appears to be defective under prion infection ¹²⁸.

5.2. A hub in developmental signalling pathways

At a mechanistic level, we reported on altered cell cycling and reduced expression of Cyclin D1 after knockdown of PrP^C in a neuronal progenitor cell line ¹⁵. These changes may notably be accounted for by defects in the Hedgehog pathway, that we identified *in vitro* and further confirmed *in vivo* within a narrow time-window during embryonic development ¹⁵. Another important clue to the PrP^C-Hedgehog connection is the location of PrP^C at the base of the primary cilium, where Hedgehog signalling operates ¹²⁹, highlighting a potential role for PrP^C in primary cilium turnover ¹⁵. It is of note that PrP^C was found in the proteome of the primary cilium in three independent studies ¹³⁰⁻¹³², calling for a better knowledge of the function exerted by PrP^C in this specific organelle. Beyond the Hedgehog pathway, we recently added another piece to the PrP-stem cell

puzzle by uncovering a connection between PrP^C and the Notch pathway ¹³³. We found that the absence of PrP^C in neural progenitors is associated with a marked reduction in the expression of various effectors of the Notch pathway, which plays an overriding role in neural stem cell maintenance ¹³⁴. This correlates with subtle differences in the developing nervous system of *Prnp* knockout mice, including transient decreases in the expression of the neural stem cell marker Nestin, and altered distribution of N-cadherin, which is important for the maintenance of neural progenitors in the ventricular zone ¹³⁵. The latter observation also fits in with the proposed role of PrP^C in cell adhesion, notably during embryonic development (see section 7). Our study further allowed delineating a gene regulatory network involving PrP^C, Notch and the EGF receptor (EGFR), where PrP^C positively controls the expression of EGFR via Notch while EGFR exerts a negative feedback on both PrP^C and Notch ¹³³. Adding another layer to this network, we documented a positive feedback regulation of the Notch pathway on PrP^C. Incidentally, the Notch target gene *Hes1* was reported to bind to the *Prnp* promoter ¹³⁶ and thus represents a good candidate for relaying this process. Finally, because PrP^C, Notch and EGFR all regulate HSC self-renewal in the bone-marrow niche ^{137,138}, we may speculate that this network also operates in HSCs.

5.3. Choice of cell fate and differentiation

A corollary to the reduced self-renewal of neural progenitors in absence of PrP^C would be a precocious engagement into a more mature state. This notion is supported by the increase in Doublecortin-positive neuroblasts in *Prnp*-null mice ¹²³. The absence of PrP^C further promotes an increase in NG2⁺Olig2⁺ oligodendrocyte precursor cells, both during embryonic development and in the adult brain ¹³⁹. In line with the notion that Notch signalling negatively regulates Olig2 expression during brain patterning ¹⁴⁰, we proposed that Notch pathway alterations may account for the increased Olig2

expression in the neural tube of PrP-null embryos ¹³³. Curiously, while PrP^C is necessary for the maintenance of neural progenitor cells in an immature state, it is on another hand required for the early steps of neurite elongation ⁶⁵ and subsequent neuronal differentiation (see section 4.2). One explanation for this apparent discrepancy would be the multiplicity of PrP^C isoforms, likely endowed with specific – or even opposite - functions. We may also suspect the involvement of defined partners, which would engage preferentially with a subset of PrP^C isoforms. Although much speculative at present, such a view is nevertheless supported by the reported competitive action of the two PrP^C ligands STI1 and A β for the recruitment of protective and toxic pathways, respectively ¹⁴¹. Apart from neurons, high levels of PrP^C were shown to enhance the development of astrocytes ¹⁴². Finally, PrP^C is differentially regulated according to cell fate along the hematopoietic lineage as well (reviewed in ^{39,42}). For instance, PrP^C expression is decreased along erythroid differentiation ¹⁴³. In this context, it is noteworthy that mutant goats naturally devoid of PrP^C exhibit elevated red blood cell number ¹⁴⁴.

6. A broad protective role against stress

6.1. PrP^C is induced under stress

Dissecting the regulation of a given gene can teach us about the function of the corresponding protein. In the case of PrP^C, several analyses of the *Prnp* promoter have notably revealed binding sites for various transcription factors, including Sp1 and AP-1 ¹⁴⁵, p53 ¹⁴⁶, the heat shock factor HSF1 ¹⁴⁷, sXBP1 ¹⁴⁸ or FOXO3A ¹⁴⁹. Interestingly, Qin et al. ¹⁵⁰ reported on the induction of PrP^C expression by Sp1 and p53 following the activation of the ATM kinase under oxidative stress conditions. In line with this, the PrP^C protein content was shown to correlate with altered redox states in prostate spheroids

¹⁵¹. The Sp1 transcription factor, which is positively regulated by the hypoxia-inducible factor HIF α was also proposed to account for the induction of PrP^C under hypoxic conditions ¹⁵². The upregulation of PrP^C in response to hypoxia has been further corroborated by diverse studies ^{18,153}. The regulation of the *Prnp* gene by sXBP1 was on another hand shown to promote PrP^C expression under ER stress conditions ^{148,154}. As for the control of *Prnp* gene expression by FOXO3A, it may notably have relevance as to contribution of PrP^C to the long-term maintenance of HSCs since FOXO3A is essential for this process ¹⁵⁵. A FOXO3A-dependent induction of PrP^C could also possibly account for the protection afforded by FOXO3A in HSCs against oxidative DNA damage ¹⁵⁶. In addition to these findings, an interesting observation is the upregulation of PrP^C in neutrophils after systemic exposure to LPS, which was shown to involve TGF β and glucocorticoids ¹⁵⁷. The latter study hints at a potential role of PrP^C in the response to neuroimmunoendocrine stress. In agreement, PrP^C was recently shown to mitigate the inflammatory response to LPS ¹⁵⁸.

6.2. Protection against oxidative stress

That PrP^C protects against oxidative stress is a recurring theme in PrP^C function and has been addressed in several reviews ^{9,92,159,160}. A global notion is that PrP^C may take part to antioxidant defence either by directly buffering ROS ¹⁶¹, undergoing processing within its N-terminal region (so-called beta-cleavage) ^{162,163} or by promoting the induction of antioxidant enzyme activities and increasing glutathione levels ^{89,124,164}. These actions are directly connected to the copper-binding capacity of PrP^C and depend on its N-terminal domain ¹⁶⁰. The protective action of PrP^C against oxidative stress is not restricted to neurons, but was also reported in various cell contexts including astrocytes ⁸⁴, MSCs ¹²⁴ or the placenta ¹⁷. This function underlies, at least partly, the beneficial role exerted by PrP^C under hypoxic conditions ^{18,124}.

6.3. Protection against genotoxic stress

The beneficial action of PrP^C against oxidative stress extends to the protection against reactive oxygen species-induced DNA damage ^{165,166} and also involves the N-terminal domain of the protein ¹⁶⁶. Recently, Bravard et al. brought further insight into the relationship between PrP^C and the DNA damage response by demonstrating that *PRNP* gene transcription is upregulated in neurons after exposure to a genotoxic stress ¹⁶⁷. The resulting increased PrP^C was shown to accumulate in the nucleus, where it interacts with the endonuclease APE1 and stimulates its base excision repair activity. The involvement of PrP^C in protection against genotoxic stress is also supported by its positive regulation by the ATM kinase ¹⁵⁰, a major guardian of genome integrity ¹⁶⁸.

6.4. Protection against apoptosis

The protective role exerted by PrP^C against other types of deleterious inputs has been extensively exemplified in various settings (see ^{159,169} for review). The pro-survival action of PrP^C has notably been documented in the context of serum deprivation ¹⁷⁰, caspase activation by staurosporine ¹⁷¹⁻¹⁷³, protein synthesis inhibition ¹⁷⁴, calcium overload ¹⁷², ischemia ^{18,40,125,126} or excitotoxicity ^{95,97-99}. From a mechanistic point of view, the cytoprotective role of PrP^C is imparted by its N-terminal domain ^{99,125,171,175} (see also section 4.3). It may relate to its mobilization by STI1 ^{68,127,176,177}, and the downstream activation of PI3K/Akt ^{126,175} or PKA ⁶⁸. An alternative mode of action relies on the shedding of the soluble N1 fragment and the downregulation of p53 ¹⁷¹.

6.5. An immune privilege molecule ?

These well-established cytoprotective actions of PrP^C together with its high and regulated expression in the immune system led to the proposal that it may contribute to immune quiescence ⁴². Immune quiescence, also termed immune privilege, encompasses a combination of anatomical, physical and immunoregulatory processes that restrain

immune-mediated inflammation in sites where it may cause irreversible damage ¹⁷⁸. The PrP^C-immune privilege connection is supported by the abundant expression of PrP^C in tissues with immune privilege, such as the brain and the placenta, together with a set of observations highlighting that the absence of PrP^C aggravates pathology in various experimental inflammatory settings ⁴². The concept that PrP^C may be considered as an immune privilege molecule provides a new angle for investigating PrP^C function and will certainly constitute an interesting area for future research.

6.6. Involvement in proteostasis

Proteostasis refers to the global network allowing for cellular proteins to maintain a proper biological activity according to the cell environment ¹⁷⁹. A strong indicator that PrP^C may contribute to the proteostatic network is the regulation of *Prnp* gene transcription by various factors of this network ¹⁷⁹, such as HSF1 ¹⁴⁷, sXBP1 ¹⁴⁸ or FOXO3A ¹⁴⁹. In addition, in terms of protein translation, one interesting observation is that in the course of TSEs, while activation of the PERK pathway halts the translation of most proteins, including synaptic constituents, *Prnp* transcripts escape this negative regulation ⁷³. From a functional point of view, PrP^C may take part to the proteostatic network at several levels: by promoting protein synthesis via mTOR ¹⁸⁰, activating autophagy by recruiting Beclin1 ¹⁸¹ or mediating the action of the cholinergic alpha7nAChR ¹⁰⁵, organizing the interplay between exosome secretion and autophagosome formation ⁸⁶ or protecting against ER stress ¹⁸². Finally, the location of PrP^C at the base of the primary cilium and its potential impact on ciliary turnover ¹⁵ may also have relevance as to this issue in view of the emerging relationship between cellular proteostasis and ciliogenesis ¹⁸³.

7. Cell adhesion and ECM contacts

7.1. Multiple adhesion partners

The involvement of PrP^C in cell adhesion was first supported by the demonstration that it interacts with several proteins relevant to this process such as the ECM molecules laminin^{63,184} or vitronectin⁷⁰, or several transmembrane proteins such as the laminin receptor precursor¹⁸⁵ or NCAM¹⁸⁶. PrP^C has further been shown to interact with β 1 integrins^{71,187} and to modulate their activity^{65,188}. This interplay with integrins may endow PrP^C with the capacity to regulate the turnover of focal adhesions^{65,189}. The contribution of PrP^C to cell adhesion processes may further involve homophilic interactions, as suggested for instance in the case of brain endothelial cells²¹.

7.2. Special links with cadherins

Cadherins represent another class of adhesion molecules sustaining cell-cell contacts whose functional interactions with PrP^C have received much interest. In intestinal cells, which form a highly polarized epithelium, PrP^C was found to co-localize with E-cadherin at cell-cell junctions¹⁹⁰. While E-cadherin did not co-precipitate with PrP^C in that study, it is noteworthy that PrP^C was however found in the interactome of E-cadherin¹⁹¹. Subsequent reports suggested that, according to cell density, PrP^C may shuttle between the membrane, where it interacts with desmosomal proteins, and the nucleus, where it regulates the transcriptional activity of β -catenin^{192,193}. These observations are consistent with a role for PrP^C in the balance between proliferation and differentiation of intestinal epithelial cells. They are further in line with the reported alteration in the intestinal epithelial barrier in PrP null mice and the decreased levels of PrP^C in the intestine of patients with inflammatory bowel diseases¹⁹⁴. Besides, in the context of embryonic development, the seminal study by Malaga-Trillo demonstrated that the lethal phenotype obtained upon knockdown of *PrP-1* in zebrafish correlated with

impaired delivery of E-cadherin at the cell surface ⁴⁶. PrP^C actually appears to broadly affect the cycling of E-cadherin since it also negatively controls its endocytosis via src kinases ¹⁹⁵. A second member of the cadherin family, namely N-cadherin, may also be influenced by PrP^C, in terms of trafficking to the neuronal cell surface ¹⁹⁶ or distribution in the developing neuroepithelium ¹³³.

7.3. Modulating the ECM composition

Finally, PrP^C may impact on the composition of the ECM itself, as described in astrocytes ⁸³ or neuronal progenitor cells ⁶⁵, or on its remodelling, for instance by controlling the activity of the metalloprotease MMP9 ¹⁹⁷. Another context where we may suspect PrP^C to act on the ECM composition is in dental tissue in view of the defects in dentin structure reported in *Prnp*-knockout mice ¹⁹⁸.

8. From partners to cell signalling

8.1. Cell signalling: the unifying function of PrP^C ?

The involvement of PrP^C in such a broad range of biological processes raises the question as to how these heterogeneous roles can be unified. A consensual view is to consider PrP^C from a cell communication point of view: its interaction with a given set of partners within a given cell environment will mobilize signal transduction cascades. In this paradigm, PrP^C will serve as a “hub”, connecting an input to cell adaptation. This function may operate according to different modes of action: in some instances PrP^C (or its cleavage products) would serve as a ligand, as described for the activation for Adgrg6 ⁴⁵, while in others it may act as a cell-surface receptor or co-receptor, as reported in the case of the A β -PrP^C-mGluR5 complex ¹⁹⁹. Finally, PrP^C may also indirectly regulate the activity of various signalling molecules such as β 1 integrins ⁶⁵, E-cadherin ⁴⁶ or EGFR ²⁰⁰ by impinging on their trafficking.

8.2. A great variety of partners

A plethora of PrP^C partners have been identified through various methods (see ^{9,201} for review), including using proteomics-based strategies ^{187,202,203}. Among those, a subset whose interaction with PrP^C was shown to have functional relevance is listed in Table 1. Two of the most studied PrP^C interacting molecules until now are the extracellular chaperone STI1 and the amyloid peptide A β , involved in Alzheimer's disease. STI1 was initially identified as a PrP^C ligand through complementary hydrophathy ²⁰⁴. Subsequent studies have highlighted an involvement of the PrP^C-STI1 duo in multiple biological processes including neural stem cell self renewal ¹²², neuronal differentiation ^{68,69}, neuronal survival ^{68,177}, neuronal protein synthesis ¹⁸⁰, memory consolidation ²⁰⁵, potentiation of neurotransmitter release ⁹⁴, or protection against ischemia ^{127,176}. As mentioned above, STI1 may further protect against the toxicity of the PrP^C alternative ligand A β ¹⁴¹. A β has entered the PrP^C field more recently, with the seminal report by Lauren et al. that PrP^C serves as a receptor for A β -derived diffusible ligands (ADDLs) and partially relays their toxicity ²⁰⁶. The A β -PrP^C interplay now represents an area of intense research and has been the topic of several recent reviews ²⁰⁷⁻²⁰⁹. Of note, some studies anterior to the Lauren paper had identified the A β precursor protein APP or its paralogues APLP1 and APLP2 as PrP^C partners ^{203,210}. From a functional point of view, the interaction of APP with PrP^C was shown to be conserved from zebrafish to human and to contribute to cell adhesion and CNS development ²¹¹. Another central PrP^C partner that deserves special attention is the scaffold protein caveolin-1. Caveolin-1 not only serves as a relay for the activation of src kinases downstream from PrP^C ^{71,94,212}, but is also involved in regulating the balance between exosomes and autophagosomes ⁸⁶. Caveolin may actually act as a bridging molecule between PrP^C and several of its binding partners: cell signalling effectors such as src kinases ^{71,94,212} or β -catenin ^{192,213}, integrins

⁷¹, cytoskeletal components such as actin ^{193,214}. The reader is referred to Table 1 for other relevant PrP^C interacting molecules.

8.3. Overview of PrP^C-dependent signal transduction

The involvement of PrP^C in cell signalling events has been addressed in several recent reviews, with special focus on neuronal ^{101,215} or immune ⁴² contexts. We further refer the reader to these reviews for a list of PrP^C downstream targets. Mechanistically, it is now generally accepted that the mobilization of signalling cascades by GPI-anchored PrP^C relies on the formation of multimolecular complexes in specific subdomains of the plasma membrane known as lipid rafts. The participation of raft constituents such as caveolin ^{71,94,212} or flotillin ²¹⁶ has been documented in some studies and is suspected in some others, where raft integrity is an important parameter ^{217,218}. In this line, it is noteworthy that the removal of sialic acid within the GPI anchor interferes with the targeting of PrP^C to the synapse ²¹⁹, directs PrP^C to a subset of rafts distinct from those where it normally segregates and hinders its activation of the cytosolic form of phospholipase A2 ²²⁰. Thus, compartmentalization represents an important parameter with respect to PrP^C signalling, which may provide spatial proximity or, to the opposite, insulation between PrP^C and its effectors. This notion is all the more important since prion infection may alter the spatial organisation and composition of rafts ^{221,222}. Endocytosis represents a connected issue, with relevance to signal duration and formation of signalling endosomes ²²³. Although little explored until now, PrP^C endocytosis was shown to be important for the recruitment of ERK1/2 in response to STI1 ²²⁴. The cell surface residency of PrP^C was further reported to be increased in cells exposed to A β ²²⁵, while decreased in prion infected cells ²²⁶. Another interesting point is the notion that PrP^C-dependent signalling may necessitate the formation of PrP^C dimers ^{99,227} and in turn favour proteolytic processing ^{93,228}. Metal and ligand binding,

internalisation and cleavage may actually be intertwined processes that clearly deserve further investigation.

Finally, despite tremendous progress in the PrP^C signalling field, several grey areas remain. One unresolved question relates to the subset of PrP^C isoforms that specifically engages into a given signalling platform, according to the cell type or even according to the sub-cellular location, as in the case of neuronal cell bodies versus neurites ^{94,212}. Delineating the mechanisms imparting spatial and temporal control on PrP^C signalling also feature among the priority axes for future investigations, since their deregulation is likely to contribute to the deleterious action of pathogenic prions ²²⁹ or other amyloid peptides such as A β (see ²³⁰ for review).

9. Concluding remarks

Because it fulfils myriads of functions and at the same time appears to be dispensable for normal development and most physiologic processes, PrP^C is both a tricky and fascinating molecule. Recent years have witnessed important advance in our understanding of the cellular and molecular pathways to which PrP^C contributes and we may expect exciting new discoveries in the coming years. Achieving a comprehensive picture of PrP^C biological role goes well beyond curiosity as it may have implications for the development of drugs aimed at restoring PrP^C functions in TSEs and other pathological settings.

Table 1

Protein name	Biological outcome
Extracellular ligands	
STI1	Neural stem cell self renewal ¹²² , Neuronal differentiation ^{68,69} , Neuronal survival ^{68,177} , Neuronal protein synthesis ¹⁸⁰ , Memory consolidation ²⁰⁵ , Potentiation of neurotransmitter release ⁹⁴ , Protection against ischemia ^{127,176} .
A β	Neurotoxicity ²⁰⁶ , NMDA turnover ²³¹ , Tau phosphorylation ²³²
ECM proteins	
Laminin	Neurite outgrowth ^{63,67,69} , Memory ²³³ .
Vitronectin	Neurite outgrowth ⁷⁰
Scaffold proteins	
Caveolin-1	Activation of src kinases downstream from PrPC ^{71,94,212} , Balance between exosomes and autophagosomes ⁸⁶
Flotillin	Trafficking of N-cadherin ¹⁹⁶ , Trafficking of EGFR ²⁰⁰ .
Cell adhesion receptors	
APP	Cell adhesion and CNS development ²¹¹ .
Integrin β 1	Neuritogenesis ^{65,70,71} .
37kDa/67kDa Laminin receptor	Cell survival ²³⁴ .
NCAM	Neurite outgrowth ⁶⁶ , Neuronal differentiation ¹²³
Growth factor receptors	
EGFR	Cell proliferation ²³⁵ .
Focal adhesion components	
Desmosomal proteins	Maintenance of epithelial polarity ¹⁹³
Neurotransmitter receptors	
mGluR1	Neurite outgrowth ⁶⁷
mGluR2	Astrocytic lactate transport ⁸⁸
mGluR5	Neurite outgrowth ⁶⁷ Long-term depression ²³⁶ , A β -dependent neurotoxicity ¹⁹⁹
mGluR6/7	Protection against excitotoxicity ²³⁷
GluA1, GluA2	Neuronal zinc transport ⁹⁶
GluN2D	Protection against excitotoxicity ²³⁸
α 7nAChR	Regulation of autophagy ¹⁰⁵ Calcium signalling ¹⁰⁴
Miscellaneous cell surface proteins	
LRP1	Endocytosis ²³⁹ ,

	Potential of neurotransmitter release ⁹⁴ .
Adgrg6	Peripheral myelin maintenance ⁴⁵
Na ⁺ /K ⁺ -ATPase	Astrocytic lactate transport ⁸⁸
Glypican-1	Raft association ²⁴⁰ ,
TNAP	Laminin dephosphorylation ¹¹⁰
BACE1	APP cleavage ²⁴¹
Miscellaneous intracellular proteins	
Members of the Rab family of small GTPases	PrP ^C trafficking ²⁴²
Argonaute	MicroRNA processing ²⁴³
Lactate dehydrogenase A (LDHA)	Activation of LDHA ²⁴⁴
β-catenin	Transcriptional activity of the β-catenin/TCF7L2 complex ¹⁹²

Legend to Figure 1:

Secondary structure of mouse PrP^C emphasizing the N-terminal flexible tail and the C-terminal globular domain. N1 and C1 fragments are generated following alpha-cleavage. N-glycosylation sites and cysteine disulfide bridge formation are indicated. Beta sheets and alpha helices are highlighted in red and green, respectively, while the hydrophobic domain is highlighted in purple.

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