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## PrPC signalling in neurons: From basics to clinical challenges

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**Abstract:** The cellular prion protein PrPC was identified over twenty-five years ago as the normal counterpart of the scrapie prion protein PrPSc, itself the main if not the sole component of the infectious agent at the root of Transmissible Spongiform Encephalopathies (TSEs). PrPC is a ubiquitous cell surface protein, abundantly expressed in neurons, which constitute the targets of PrPSc-mediated toxicity. Converging evidence have highlighted that neuronal, GPI-anchored PrPC is absolutely required for prion-induced neuropathogenesis, which warrants investigating into the normal function exerted by PrPC in a neuronal context. It is now well-established that PrPC can serve as a cell signalling molecule, able to mobilize transduction cascades in response to interactions with partners. This function endows PrPC with the capacity to participate in multiple neuronal processes, ranging from survival to synaptic plasticity. A diverse array of data have allowed to shed light on how this function is corrupted by PrPSc. Recently, amyloid A $\beta$  oligomers, whose accumulation is associated with Alzheimer's disease (AD), were shown to similarly instigate toxic events by deviating PrPC-mediated signalling. Here, we provide an overview of the various signal transduction cascades ascribed to PrPC in neurons, summarize how their subversion by PrPSc or A $\beta$  oligomers contributes to TSE or AD neuropathogenesis and discuss the ensuing clinical implications.

Opposed Reviewers:

Dear Dr Forest,

Thank you for your letter of June 3rd 2014 regarding our review entitled « **PrP<sup>C</sup> signalling in neurons: from basics to clinical challenges** ». I am pleased to provide a revised version of our review, which takes into account the reviewers' comments. I hope this review is now suitable for publication in Biochimie.

Yours sincerely,

Dr S. Mouillet-Richard  
INSERM UMR-S1124, Université Paris Descartes,  
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Detailed answer to the reviewers:

We thank the reviewers for their positive comments.

As pointed by reviewer 3, we have corrected some errors within the text.

We have taken into account the minor modifications suggested by reviewer 4:

1. *In fig. 2, the interaction with <math>\alpha</math>7nAChR could be addressed in the scheme, since it is an important regulator of STII-PrP signal transduction complex Beraldo et al., J Biol Chem. 2010 Nov 19;285(47):36542-50.*

The interaction of PrP<sup>C</sup> with the alpha7nAChR is now presented in Fig.2

2. *Provide reference for the statement "This signal, which can be revealed in response to antibody-mediated ligation of PrPC, also occurs upon binding of PrPC to its endogenous ligands STII (Line 13 - 18, page 8)".*

The corresponding reference is now inserted at the end of the sentence.

3. *The subtitle of section 5 does not seem to be appropriate since the section mainly addresses the transmembrane proteins responsible for transducing PrPC signaling into intracellular compartments. Temporal alterations of PrPC signaling cascades were not discussed.*

The subtitle of section 5 has been changed into "PrP<sup>C</sup> signalling partners at the membrane".

Author agreement form for

**PrP<sup>c</sup> signalling in neurons: from basics to clinical challenges**

by Théo Z. Hirsch, Julia Hernandez-Rapp, Séverine Martin-Lannerée, Jean-Marie Launay and Sophie Mouillet-Richard

Material submitted is original, all authors are in agreement to have the article published

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4 **PrP<sup>C</sup> signalling in neurons: from basics to clinical challenges**  
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7 **Théo Z. Hirsch<sup>1,2</sup>, Julia Hernandez-Rapp<sup>1,2,3</sup>, Séverine Martin-Lannerée<sup>1,2</sup>, Jean-Marie**  
8 **Launay<sup>4,5</sup> and Sophie Mouillet-Richard<sup>1,2,\*</sup>**  
9

10  
11 **Abstract**  
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13  
14 The cellular prion protein PrP<sup>C</sup> was identified over twenty-five years ago as the normal  
15 counterpart of the scrapie prion protein PrP<sup>Sc</sup>, itself the main if not the sole component of  
16 the infectious agent at the root of Transmissible Spongiform Encephalopathies (TSEs). PrP<sup>C</sup>  
17 is a ubiquitous cell surface protein, abundantly expressed in neurons, which constitute the  
18 targets of PrP<sup>Sc</sup>-mediated toxicity. Converging evidence have highlighted that neuronal, GPI-  
19 anchored PrP<sup>C</sup> is absolutely required for prion-induced neuropathogenesis, which warrants  
20 investigating into the normal function exerted by PrP<sup>C</sup> in a neuronal context. It is now well-  
21 established that PrP<sup>C</sup> can serve as a cell signalling molecule, able to mobilize transduction  
22 cascades in response to interactions with partners. This function endows PrP<sup>C</sup> with the  
23 capacity to participate in multiple neuronal processes, ranging from survival to synaptic  
24 plasticity. A diverse array of data have allowed to shed light on how this function is  
25 corrupted by PrP<sup>Sc</sup>. Recently, amyloid A $\beta$  oligomers, whose accumulation is associated with  
26 Alzheimer's disease (AD), were shown to similarly instigate toxic events by deviating PrP<sup>C</sup>-  
27 mediated signalling. Here, we provide an overview of the various signal transduction  
28 cascades ascribed to PrP<sup>C</sup> in neurons, summarize how their subversion by PrP<sup>Sc</sup> or A $\beta$   
29 oligomers contributes to TSE or AD neuropathogenesis and discuss the ensuing clinical  
30 implications.  
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Highlights Hirsch et al.

- Prion diseases are caused by the conversion of PrP<sup>C</sup> into its scrapie PrP<sup>Sc</sup> isoform.
- PrP<sup>C</sup> can act as a cell surface receptor able to instruct signalling events.
- PrP<sup>Sc</sup> exerts its toxicity by subverting PrP<sup>C</sup>-dependent signalling cascades in neurons.
- PrP<sup>C</sup> may transduce toxic signals after binding to A $\beta$  oligomers.
- Targeting PrP<sup>C</sup>-associated pathways may alleviate prion and Alzheimer's diseases.

# PrP<sup>C</sup> signalling in neurons: from basics to clinical challenges

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## Abstract

1  
2 The cellular prion protein PrP<sup>C</sup> was identified over twenty-five years ago as the normal  
3  
4 counterpart of the scrapie prion protein PrP<sup>Sc</sup>, itself the main if not the sole component  
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6 of the infectious agent at the root of Transmissible Spongiform Encephalopathies (TSEs).  
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8 PrP<sup>C</sup> is a ubiquitous cell surface protein, abundantly expressed in neurons, which  
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10 constitute the targets of PrP<sup>Sc</sup>-mediated toxicity. Converging evidence have highlighted  
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12 that neuronal, GPI-anchored PrP<sup>C</sup> is absolutely required for prion-induced  
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14 neuropathogenesis, which warrants investigating into the normal function exerted by  
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16 PrP<sup>C</sup> in a neuronal context. It is now well-established that PrP<sup>C</sup> can serve as a cell  
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18 signalling molecule, able to mobilize transduction cascades in response to interactions  
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20 with partners. This function endows PrP<sup>C</sup> with the capacity to participate in multiple  
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22 neuronal processes, ranging from survival to synaptic plasticity. A diverse array of data  
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24 have allowed to shed light on how this function is corrupted by PrP<sup>Sc</sup>. Recently, amyloid  
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26 A $\beta$  oligomers, whose accumulation is associated with Alzheimer's disease (AD), were  
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28 shown to similarly instigate toxic events by deviating PrP<sup>C</sup>-mediated signalling. Here, we  
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30 provide an overview of the various signal transduction cascades ascribed to PrP<sup>C</sup> in  
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32 neurons, summarize how their subversion by PrP<sup>Sc</sup> or A $\beta$  oligomers contributes to TSE  
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34 or AD neuropathogenesis and discuss the ensuing clinical implications.  
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**Keywords:** Prion protein, cell signalling, neurons, A $\beta$ , prion diseases, Alzheimer's  
disease



**Abbreviations:** AD, Alzheimer's disease; APP, amyloid precursor protein; cPLA2, cytosolic phospholipase A2; GPI, glycosylphosphatidylinositol; GPCR, G-protein coupled receptor; GSK3 $\beta$ , glycogen synthase kinase 3  $\beta$ ; Ln $\gamma$ 1, laminin  $\gamma$ 1 chain; LRP-1, low-density lipoprotein-related protein 1; LTD, long-term depression; LTP, long-term potentiation; mTOR, mammalian target of rapamycin; NCAM, neural cell adhesion molecule; PDK1, phosphoinositide-dependent kinase 1; PI3K, phosphoinositide 3 kinase; PKA, protein kinase A; PLC, phospholipase C; PrP<sup>C</sup>, cellular prion protein; PrP<sup>Sc</sup>, scrapie prion protein; PSD, postsynaptic density; ROS, reactive oxygen species; STI-1, stress-inducible protein 1; TACE, TNF $\alpha$ -converting enzyme; TSE, Transmissible Spongiform Encephalopathies; UPR: unfolded protein response;

## 1. Introduction

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2  
3 The cellular prion protein PrP<sup>C</sup> has received considerable attention due to its central  
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5 role in the development of Transmissible Spongiform Encephalopathies (TSEs). These  
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7 fatal neurodegenerative disorders arise from the autocatalytic conversion of PrP<sup>C</sup> into  
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9 its aggregate-prone conformational variant PrP<sup>Sc</sup>, standing for scrapie isoform of the  
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11 prion protein [1]. PrP<sup>Sc</sup> actually constitutes the only identified component of the  
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13 infectious TSE agent, which propagates by acting as a seed to promote the template-  
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15 directed misfolding of endogenous PrP<sup>C</sup> [1]. Accordingly, PrP-null mice fail to develop  
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17 TSE upon prion inoculation [2]. PrP<sup>C</sup> is a normal host-encoded protein of about 230  
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19 residues, present in all cell types and most abundantly found in neurons [3]. PrP<sup>C</sup>  
20  
21 possesses a glycosylphosphatidylinositol (GPI) anchor that sustains its attachment to  
22  
23 the plasma membrane and can be hydrolyzed by endogenous phospholipases to yield  
24  
25 secreted PrP<sup>C</sup> (see Fig. 1) [4, 5]. Its main features include the presence of octapeptide  
26  
27 repeats in the unstructured N-terminal region, involved in the binding of divalent  
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29 cations such as copper [6] or zinc [7], as well as a disulfide bond encompassing two  
30  
31 asparagine residues that can be potentially N-glycosylated [8]. PrP<sup>C</sup> can undergo several  
32  
33 proteolytic cleavages: (i) in the octarepeat region (beta-cleavage), (ii) at position  
34  
35 111/112 (alpha-cleavage) or (iii) in the extreme C-terminus to generate an anchorless  
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37 isoform (reviewed in [5, 9], [10]). The so-called alpha cleavage, giving rise to the N1 N-  
38  
39 terminal and the C1 C-terminal fragments, has been most extensively studied as it  
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41 occurs physiologically, notably in the brain [11] and because it precludes the conversion  
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43 into pathological PrP<sup>Sc</sup> [12]. Thus, while often referred to as a unique entity, PrP<sup>C</sup>  
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45 actually encompasses a great diversity of isoforms, whose distribution may vary  
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47 according to the cell type and whose respective functions await further investigation [3].  
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Like many GPI-anchored protein, PrP<sup>C</sup> segregates in sphingolipid-rich membrane microdomains known as "lipid-rafts" (reviewed in [13]). These specialized subcellular compartments are enriched in receptors, second messengers and effectors and are considered as "signal transduction centres" [14]. Over the past fifteen years, evidence has accumulated that PrP<sup>C</sup> can act as a cell surface receptor, co-receptor or ligand, able to recruit downstream signal transduction pathways. Such function is thought to be driven by the interaction of PrP<sup>C</sup> with promiscuous partners, within multimolecular complexes [3]. Among the vast array of PrP<sup>C</sup> interactors and effectors in different cell types and tissues, special interest is devoted to those that may play a role in prion-induced neurotoxicity. Indeed, it is now well-acknowledged that pathogenic prions exert their deleterious action by subverting the normal function of PrP<sup>C</sup> in the brain [15]. Their toxicity is fully dependent on the expression of PrP<sup>C</sup> in neurons [16, 17] and requires that it is GPI-anchored [18]. Deciphering how PrP<sup>Sc</sup> deviates PrP<sup>C</sup>-dependent signalling cascades is attracting all the more attention since this pathogenic mechanism appears to be also at play in Alzheimer's disease (AD), with amyloid A $\beta$  oligomers hijacking PrP<sup>C</sup>-dependent pathways to instigate toxic events (reviewed in [19]).

In the present review, we summarize the current knowledge of PrP<sup>C</sup>-dependent signalling in neurons, its pathophysiological implications and highlight some therapeutic prospects to alleviate TSE and AD-related pathogenesis.

## 2. How is PrP<sup>C</sup> signalling initiated?

A current view is that the mobilization of PrP<sup>C</sup>-mediated cell signalling events occurs in response to the association of this protein with various partners at the plasma membrane [3], a typical scheme for GPI-anchored proteins [14]. Indeed, in neurons as in

1 other cell types, the majority of PrP<sup>C</sup> molecules are GPI-anchored, which drives their  
2 subcellular localization in lipid rafts [13]. Two transmembrane variants of PrP<sup>C</sup> have  
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4 further been described that are associated with neurodegeneration and whose  
5 physiological relevance remains elusive [20]. Beyond rafts, PrP<sup>C</sup> is also found in  
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7 postsynaptic densities (PSDs) [21], which may associate with postsynaptic membrane  
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9 rafts [22]. The special composition of these compartments allows the spatial segregation  
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11 of receptors and signal transduction effectors and favours their effective interaction  
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13 [23]. Classically, the mobilization of signalling cascades by GPI-anchored proteins is  
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15 induced by their clustering in response to ligand binding [23]. Such clustering can be  
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17 triggered by antibody-mediated ligation, an experimental paradigm that allowed our  
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19 laboratory to unveil various PrP<sup>C</sup>-dependent cascades in neuronal cells [24-27]. Data  
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21 from the Tazelt laboratory further established that the recruitment of neuroprotective  
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23 signals by PrP<sup>C</sup> necessitates its dimerization via its hydrophobic domain (residues 113-  
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25 133) [24]. Interestingly, PrP<sup>C</sup> dimerization appears to enhance its alpha-cleavage and  
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27 production of the N1 fragment [25] as well as its shedding [26]. PrP<sup>C</sup> cleavage may  
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29 additionally be influenced by the binding of copper [10], which also impacts on PrP<sup>C</sup>  
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31 trafficking and signalling activity [6, 27]. Shed PrP<sup>C</sup> may act in cis or in trans to  
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33 homodimerize [28], interact with the neural cell adhesion molecule NCAM [29] or  
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35 putatively other yet-to-be-identified cell surface molecules [30, 31]. Besides,  
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37 physiologically relevant interactions of PrP<sup>C</sup> with several extracellular molecules, acting  
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39 as ligands, have been documented and are summarized in (Fig. 1). These include the  
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41 matrix components vitronectin and laminin or the extracellular chaperone stress-  
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43 inducible protein 1 (STI-1), whose binding to PrP<sup>C</sup> causes reciprocal conformational  
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45 changes [32]. The repertoire of PrP<sup>C</sup> interactors also includes the amyloid precursor  
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47 protein APP [33, 34] and its aggregation-prone cleavage product A $\beta$  [19, 35] (see Fig. 1),  
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1 whose unbalanced production lies at the root of AD, according to the amyloid cascade  
2 hypothesis [36]. While it is unclear whether the PrP<sup>C</sup>-APP interaction instructs  
3 downstream cell signalling events or whether the binding of PrP<sup>C</sup> to A $\beta$  may occur under  
4 physiological conditions, it is now well-established that A $\beta$  oligomers bind to PrP<sup>C</sup> in AD  
5 brain [37] and subvert PrP<sup>C</sup>-dependent signalling cascades to affect various neuronal  
6 processes (reviewed in [19]) (see below).  
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14 The multiplicity of PrP<sup>C</sup> interactors on the one hand and isoforms on the other hand  
15 raises the issue as to which PrP<sup>C</sup> entities interact with a given partner and whether  
16 several ligands may compete for binding to a given PrP<sup>C</sup> entity, as recently suggested for  
17 STI-1 and A $\beta$  oligomers [38].  
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### 28 **3. PrP<sup>C</sup> signalling in neuronal cells: a plethora of effectors**

29 The ability of PrP<sup>C</sup> to trigger cell signalling events, initially suspected from its location in  
30 lipid rafts (reviewed in [13]) and the reported ability of GPI-anchored proteins to  
31 activate src kinases [39], has been examined using multiple experimental paradigms. A  
32 well-characterized proximal effector of PrP<sup>C</sup> is Fyn, a tyrosine kinase of the src family  
33 that we first identified as a neuronal-restricted target of PrP<sup>C</sup> using the inducible  
34 neuronal 1C11 cell line [40], and that associates with PrP<sup>C</sup> to form a signalling complex  
35 [41]. In 1C11-derived differentiated cells, the PrP<sup>C</sup>-Fyn coupling is relayed by the  
36 membrane protein caveolin [40], now recognized as an important regulator of neuronal  
37 intracellular signalling [42]. The PrP<sup>C</sup>-dependent activation of Fyn was subsequently  
38 shown to be involved in NCAM-dependent neurite outgrowth in primary hippocampal  
39 neurons [29]. Apart from caveolin and NCAM, the natures of the PrP<sup>C</sup> partners that may  
40 contribute to Fyn activation in a physiological context remain to be identified. From a  
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pathological point of view, the PrP<sup>C</sup>-Fyn platform has received renewed interest in the last few years as it is hijacked both by PrP<sup>Sc</sup> [43] and by A $\beta$  oligomers [19, 44] to transduce their toxicity (see below).

In a recent study, we documented that neuronal PrP<sup>C</sup> has the capacity to recruit another member of the src kinase family, the Lyn kinase [27], previously found to be present in the plasma microenvironment of PrP<sup>C</sup> in primary cerebellar neurons [45]. This signal, which can be revealed in response to antibody-mediated ligation of PrP<sup>C</sup>, also occurs upon binding of PrP<sup>C</sup> to its endogenous ligand STI-1 [27]. Noteworthy, like Fyn, the activation of Lyn driven by PrP<sup>C</sup> is transduced via caveolin [27], further supporting a central role for caveolin in PrP<sup>C</sup>-dependent signalling.

Other reported intracellular effectors of PrP<sup>C</sup> signalling include the phosphoinositide 3 kinase (PI3K) [27, 46], Akt [27, 47], protein kinase A (PKA) [48-50], the reactive oxygen species (ROS) generating enzyme NADPH oxidase [51], the MAP kinases ERK1/2 [49-52], the glycogen synthase kinase GSK3 $\beta$  [27], the TNF $\alpha$ -converting enzyme (TACE) metalloprotease [53], the mammalian target of rapamycin mTOR [47], as well as several transcription factors: CREB, Egr-1 and c-fos [54]. Links with sphingolipid [55] and calcium signalling [56-59] have also been depicted. The diverse array of PrP<sup>C</sup> signalling effectors is summarized in Table 1.

Some of these effectors have been shown to be under the control of Fyn (e.g. NADPH oxidase) or Lyn (e.g. GSK3 $\beta$ ). Some other pathways, such as those featuring PKA, remain to be delineated. More generally, an important challenge for the next few years will be to translate the repertoire of PrP<sup>C</sup> targets into transduction cascades in relation with the initial triggering signal (e.g. STI-1 or laminin), cell type and biological response, as outlined in Fig. 2. Altogether, achieving this goal appears as a prerequisite to ultimately

1 reach a global view of the various PrP<sup>C</sup>-dependent signalling platforms and pathways,  
2 their potential crosstalks, as well as their integrated cellular outcome.  
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#### 7 **4. An intimate connection with neurotransmitter receptors**

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10 Another important class of lipid raft residents in neurons is neurotransmitter receptors  
11 [60]. A number of studies have unveiled functional interactions between PrP<sup>C</sup> and  
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13 diverse ionotropic or G-protein coupled neurotransmitter receptors, which are  
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15 summarized in Table 2. Focusing on serotonergic receptors, our laboratory reported on  
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17 the PrP<sup>C</sup>-dependent modulation of the signalling activity of 5-HT<sub>1B</sub>, 5-HT<sub>2A</sub> and 5-HT<sub>2B</sub>  
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19 receptors, all coupled to G-proteins, in serotonergic 1C11<sup>5-HT</sup> neuronal cells [61].  
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21 Interestingly, we observed both positive and negative actions of PrP<sup>C</sup>, depending on the  
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23 G-protein and pathway considered, and that the modulatory effect of PrP<sup>C</sup> depends on  
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25 caveolin [61]. Very recently, we delineated an additional link between PrP<sup>C</sup> and the 5-  
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27 HT<sub>1B</sub> receptor, by showing that the PrP<sup>C</sup>-dependent inactivation of GSK3 $\beta$  interferes  
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29 with the subcellular localization and functional activity of this receptor and thereby  
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31 potentiates neurotransmitter release [27]. Metabotropic glutamate receptors constitute  
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33 another class of G-protein coupled neurotransmitter receptors (GPCR) that has captured  
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35 much attention in relation to PrP<sup>C</sup> function. PrP<sup>C</sup> has the capacity to interact with  
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37 mGlu1AR, mGlu1BR as well as mGlu5R [56], which all belong to the Group I of  
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39 metabotropic glutamate receptors and are coupled to Gq-mediated phospholipase C  
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41 (PLC) activation [62]. Further, the recruitment of the PrP<sup>C</sup>-mGluR signalling complex by  
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43 the laminin  $\gamma$ 1 chain (Ln  $\gamma$ 1) was shown to trigger calcium release, ERK1/2 activation  
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45 and to sustain neurite outgrowth [56]. In a pathological context, mGlu5R receptors have  
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47 been reported to relay the activation of Fyn [63] and to mediate the facilitation of long  
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1 term depression (LTD) [64] in response to the binding of A $\beta$  oligomers to PrP<sup>C</sup> (see  
2 below).

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5 The capacity of PrP<sup>C</sup> to interact with neurotransmitter receptors is not restricted to  
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7 GPCRs. Indeed, it may form a complex with the ionotropic nicotinic acetylcholine  
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9 receptor  $\alpha$ 7nAChR, whose mobilization in the hippocampus by the STI-1 ligand  
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11 promotes intracellular calcium release [57]. Finally, multiple links with NMDA receptors  
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13 have been depicted, in relation with the critical involvement of these receptors in long-  
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15 term potentiation and synaptic plasticity [65]. For instance, PrP<sup>C</sup> was reported to exert a  
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17 negative regulation on GluN2D-containing NMDA receptors, thereby providing a  
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19 neuroprotective mechanism against glutamate excitotoxicity [66]. It also appears to  
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21 sustain the internalization of GluN2B-containing NMDA receptors via Fyn-mediated  
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23 phosphorylation in response to ethanol exposure [67]. Of note, several lines of evidence  
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25 indicate that the PrP<sup>C</sup>-dependent modulation of NMDA receptors is lost in the presence  
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27 of toxic oligomers, including A $\beta$ , leading to reduced receptor desensitization [44, 68, 69].  
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29  
30 Altogether, these observations substantiate an important role for PrP<sup>C</sup> in the regulation  
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32 of diverse neurotransmitter receptors, which may account for the subtle behavioural  
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34 and / or cognitive deficits reported in PrP-null mice [70]. Refining our current  
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36 knowledge of the interplay between PrP<sup>C</sup> and neurotransmitter receptors has obvious  
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38 implications for unravelling the global impact of prions or A $\beta$  oligomers on neuronal  
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40 activity and homeostasis, as will be discussed below.  
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### 53 **5. PrP<sup>C</sup> signalling partners at the membrane**

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56 Lipid rafts typically allow a tight spatial and temporal control of cell signalling events  
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58 [71]. As for PrP<sup>C</sup>-dependent signalling cascades, multiple regulatory mechanisms have  
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1 been highlighted. First, the interaction of PrP<sup>C</sup> with caveolin [40, 41], likely sustains the  
2 compartmentation of PrP<sup>C</sup> with appropriate signalling partners, e.g. src kinases or  
3 neurotransmitter receptors [42]. Adding further complexity to the picture, lipid rafts  
4 may vary in their composition [72]. Such raft heterogeneity may account for the spatial  
5 restriction of the PrP<sup>C</sup>-caveolin-Lyn complex to neuronal cell bodies, to the opposite of  
6 the PrP<sup>C</sup>-caveolin-Fyn complex, which is found in neuronal processes [27]. Whether  
7 each platform involves distinct subsets of PrP<sup>C</sup> molecules remains to be investigated.  
8 The nature of potential transmembrane partners contributing to the spatial control of  
9 PrP<sup>C</sup>-signalling complexes also deserves attention. Both NCAM [29] and mGlu5R [63]  
10 have been reported to transduce PrP<sup>C</sup>-dependent Fyn activation. Recently, we  
11 highlighted the contribution of the transmembrane low-density receptor protein 1 (LRP-  
12 1) to the recruitment of effectors downstream from the PrP<sup>C</sup>-caveolin-Lyn platform [27].  
13 LRP-1 was previously identified as a PrP<sup>C</sup> partner that regulates its internalization [73],  
14 and whose interaction with PrP<sup>C</sup> is enhanced by copper [74]. Among its multiple ligands,  
15 LRP-1 is known to interact with A $\beta$ , and recent data indicate that LRP-1 is mandatory for  
16 the PrP<sup>C</sup>-dependent toxicity of A $\beta$  [75]. Beyond favouring the interaction with LRP-1,  
17 the binding of copper to PrP<sup>C</sup> was also shown to enhance its endocytosis together with  
18 Glypican-1 [76], a GPI-anchored heparan sulfate proteoglycan that mediates the  
19 association of PrP<sup>C</sup> with lipid rafts and, in a pathological context, favours the formation  
20 of PrP<sup>Sc</sup> [77]. While it may act as a cofactor for prion conversion, whether Glypican-1  
21 modulates interactions of PrP<sup>C</sup> with partners and downstream cell signalling events  
22 remains to be investigated. The same question applies to the 37kDa/67kDa laminin  
23 receptor, reported to promote the internalization of PrP<sup>C</sup> [78] and to sustain PrP<sup>Sc</sup>  
24 propagation in prion-infected cells [79]. Whatever the partners involved, PrP<sup>C</sup>  
25 endocytosis appears to be mandatory for the recruitment of some effectors, such as the  
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1 activation of ERK1/2 in response to STI-1 [52]. Finally, as will be emphasized below,  
2 alterations in the dynamics of PrP<sup>C</sup> interactions with its partners, such as its increased  
3 cell-surface localization upon binding to A $\beta$  oligomers [80], may disrupt the strength  
4 and duration of PrP<sup>C</sup>-related signalling and instigate toxic cascades.  
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## 10 11 12 **6. Translating PrP<sup>C</sup>-mediated signalling pathways in neurons into a biological** 13 **response** 14 15

16 Overall, through the various signalling cascades brought to light in a neuronal context,  
17 PrP<sup>C</sup> appears to be connected with nearly all aspects of neuronal physiology. Its  
18 contribution to neurite outgrowth may be sustained by its interaction with NCAM and  
19 downstream Fyn activation [29], vitronectin [81], Ln  $\gamma$ 1 [82, 83] or STI-1 [50] and may  
20 also involve an interplay with integrins [41, 84]. Of note, a synergistic action of Ln  $\gamma$ 1  
21 and STI-1 in triggering PrP<sup>C</sup>-dependent calcium signalling and neuritogenesis has been  
22 described [59]. Beraldo et al. also highlighted the requirement of mGlu1R to transduce  
23 the PrP<sup>C</sup>-Ln  $\gamma$ 1-mediated induction of process outgrowth [56]. In vivo, the PrP<sup>C</sup>-Ln  $\gamma$ 1  
24 interaction was shown to modulate memory consolidation, with a suggested implication  
25 of PKA and ERK1/2 [85]. This property is shared by the PrP<sup>C</sup>-STI-1 duo [86], which also  
26 sustains protein synthesis through the mobilization of mTOR [47]. Interestingly, mTOR  
27 also emerges as an important player in synaptic plasticity [87], like other PrP<sup>C</sup> targets  
28 such as ERK1/2, CREB, or egr-1 [88]. Another possible signalling intermediate in these  
29 processes is the GSK3 $\beta$  kinase, which we recently identified as a downstream target of  
30 the PrP<sup>C</sup>-STI-1 coupling [27] and has been shown both to play a pivotal role in synaptic  
31 plasticity and long-term potentiation (LTP) [89] and to regulate mTOR activity [90].  
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may suspect that inhibition of this kinase instigated by the interaction of PrP<sup>C</sup> with STI-1 also contributes to the well-established neuroprotective action of these two molecules [49, 92-94].

Multiple links between PrP<sup>C</sup> and neurotransmitter-associated functions have further been uncovered. For instance, through a ROS-TACE-TNF $\alpha$  pathway, PrP<sup>C</sup> promotes bioamine degradation [53], an observation which has to be brought together with the contribution of bioamine turnover to memory consolidation [95, 96]. Our recent work further established that the negative regulation of the serotonergic 5-HT<sub>1B</sub> receptor activity downstream from the PrP<sup>C</sup>-Lyn-GSK3 $\beta$  cascade potentiates neurotransmitter release [27]. Adding to this view is the interplay between PrP<sup>C</sup> and diverse neurotransmitter receptors, as summarized above. Finally, we may note that the multifaceted contribution of PrP<sup>C</sup> to neuronal homeostasis and activity is in keeping with the wide array of alterations depicted in the context of prion infection [97-99] or after binding of A $\beta$  oligomers to PrP<sup>C</sup> (reviewed in [19]).

## 7. Causes and consequences of the subversion of PrP<sup>C</sup> signalling in neurons

That the deviation of PrP<sup>C</sup>-dependent-signalling may contribute to neurodegeneration is now well established in the case of prion infection and also in Alzheimer's disease. Prions fail to induce any pathogenesis when endogenous PrP<sup>C</sup> is selectively knocked-out in neurons [17] or is exclusively anchorless [18]. These pioneering studies have set the stage for investigating how PrP<sup>Sc</sup> may usurp PrP<sup>C</sup> normal signalling function to exert its toxic action. For instance, pathological PrP conformers were shown to induce a switch from anti-apoptotic to pro-apoptotic signalling of PrP<sup>C</sup> [24]. PrP<sup>Sc</sup> aggregation was further reported to trigger the clustering of its GPI anchors at high densities and thereby

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cause alterations in membrane composition, pathological activation of cytosolic phospholipase A2 (cPLA2) and synaptic damage [100]. In a recent work, we documented that pathogenic prions hijack the PrP<sup>C</sup>-Fyn platform to constitutively recruit downstream effectors, including NADPH oxidase, and cause impairment in the clearance of amyloid A $\beta$  [43] (Fig. 3). The former observation recalls the central role established for the NADPH oxidase subunit NOX2 in prion-induced neuronal damage [101, 102]. Altogether, these data support the notion that the conversion of PrP<sup>C</sup> into PrP<sup>Sc</sup> may promote the constitutive recruitment of proximal downstream effectors in lipid rafts. Overactivation of PrP<sup>C</sup> downstream targets may similarly account for the development of a spontaneous neurodegenerative illness in transgenic mice overexpressing PrP<sup>C</sup> by 5 to 10 fold [103]. Besides, the accumulation of PrP<sup>C</sup> in lipid raft during aging, proposed to explain the occurrence of sporadic prion diseases [104], might also amplify the activation of downstream cascades. Importantly, the pathological deviation of PrP<sup>C</sup>-mediated signalling may be further self-sustained by various subsequent alterations such as aberrant distribution of caveolin-1 [105], impaired cholesterol metabolism [106], decreased protective alpha-cleavage [107] or reduced clearance of A $\beta$  [43, 108].

The pathological implications of the subversion of PrP<sup>C</sup> function are not restricted to prion infection since PrP<sup>C</sup> can convey neurotoxic signals after binding to various types of beta-sheet rich conformers, including A $\beta$  [68]. Regarding the AD connection, converging data gathered in the last 5 years demonstrate that PrP<sup>C</sup> can act as a cell-surface receptor for oligomeric A $\beta$  (reviewed in [19]). Multiple deleterious outcomes of the interaction of A $\beta$  with PrP<sup>C</sup> have been depicted, including synaptic dysfunction and dendritic spine retraction [44], neuronal death [109], inhibition of LTP [35], exacerbation of LTD [64], axonal degeneration [110], as well as induction of autophagy [111]. From a mechanistic

1 point of view, A $\beta$  oligomers bind to PrP<sup>C</sup> at different sites within the N-terminal region  
2 (see Fig. 1) and recruit downstream effectors (Fig. 3). Among these, Fyn has captured  
3 the most attention since this kinase has long been known to be mandatory for A $\beta$ -  
4 mediated toxicity [112, 113]. In recent years, several outstanding observations have  
5 been reported, including the central role of Fyn in promoting phosphorylation of the  
6 GluN2B subunit of NMDA receptors and dendritic spine loss [44], as well as tau  
7 hyperphosphorylation [114] after engagement of A $\beta$  oligomers with PrP<sup>C</sup>. mGlu5Rs  
8 were further shown to act as co-receptors for PrP<sup>C</sup>-bound A $\beta$  oligomers to promote Fyn  
9 activation [63]. Whether this property is shared by other metabotropic or ionotropic  
10 receptors deserves to be investigated, in view of the broad implication of  
11 neurotransmitter receptors in AD pathology [115]. Adding to the above data, PrP<sup>C</sup> was  
12 also shown to relay the A $\beta$ -dependent activation of cPLA2 [116], caspase 3 [109],  
13 ERK1/2 [80], NADPH oxidase [117] and phosphoinositide-dependent kinase-1 (PDK1),  
14 itself leading to decreased TACE activity [107]. Further studies are needed to explore the  
15 relationship between these diverse events and Fyn activation. Finally, from a  
16 therapeutic perspective, it is worth noting that some studies have addressed the  
17 relevance of observations gained in vitro or in mice and have for instance established  
18 that A $\beta$  oligomers and PrP<sup>C</sup> interact in the brain of AD patients but not healthy controls  
19 [37]. The overactivation of PDK1 found in AD mouse models to be dependent on PrP<sup>C</sup>  
20 expression was corroborated in AD patients as well [107]. Overall, while PrP<sup>C</sup> certainly  
21 is not the sole relay of A $\beta$ -mediated toxicity [118], these cumulative data provide several  
22 promising avenues for therapeutic intervention in prion and Alzheimer's diseases,  
23 which are discussed below.

## 8. Therapeutic prospects

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3 At present, TSEs remain fatal diseases with no effective treatment despite numerous  
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5 trials (see [119] for example). This also holds true for AD, which represents a major  
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7 health burden with an estimated 25 million people affected worldwide. The  
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9 development of effective therapies for prion and Alzheimer's diseases faces multiple  
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11 challenges: patients are diagnosed at a stage when brain damage has already occurred,  
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13 drugs need to cross the blood-brain-barrier, and last but not least, the normal functions  
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15 of the targeted proteins need to be preserved. Beyond strategies aiming at limiting the  
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17 production and / or accumulation of PrP<sup>Sc</sup>, which will not be addressed here, one major  
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19 axis followed for the treatment of TSEs is that of immunotherapy (reviewed in [120]).  
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21 Some passive immunotherapy studies have notably demonstrated a substantial benefit  
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23 for a panel of anti-PrP<sup>C</sup> antibodies in delaying onset of disease, although whether this  
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25 strategy can still prove useful when treatment is initiated after the appearance of clinical  
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27 symptoms has yet to be demonstrated (reviewed in [120]). More recently, a subset of  
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29 the same antibodies has been tested for their ability to counteract the interaction of A $\beta$   
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31 oligomers with PrP<sup>C</sup>. In vitro, the binding of A $\beta$  oligomers to PrP<sup>C</sup> was successfully  
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33 antagonized using 6D11 [35, 44, 109, 114], ICSM35 [121] or Sha31 [122] anti-PrP<sup>C</sup>  
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35 antibodies. The 6D11 antibody was further shown to protect against cognitive deficits in  
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37 a mouse model of AD [123]. Finally, brain-derived A $\beta$ -mediated impairment of LTP  
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39 could be efficiently prevented following immunotargeting of PrP<sup>C</sup> using ICSM35 or  
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41 ICSM18 antibodies or the D13 antibody fragment (Fab) [124].  
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53 To the opposite of these studies, some antibodies targeting PrP<sup>C</sup> exhibit neurotoxic  
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55 potential. Beyond some conflicting results [125, 126], an extensive study from the  
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57 Aguzzi laboratory has allowed to map the epitopes of a panel of toxicity-inducing anti-  
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59 PrP<sup>C</sup> antibodies [102]. These neurotoxic antibodies were shown to systematically target  
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1 the globular domain (residues 124-230) - although some antibodies recognizing this  
2 region remained innocuous - and to promote neurodegeneration via calpain and NOX2  
3 activation [102], in a manner similar to infectious prions [101]. Since NADPH oxidase is  
4 a downstream effector of PrP<sup>C</sup> signalling [51] and is overactivated in prion infection  
5 [43], NOX2, as suggested above [101, 102], and putatively other NADPH oxidase  
6 subunits, may prove valuable targets to combat TSEs. The indispensable role of NOX2 in  
7 host defence would, however, need to be taken into account, should its inhibition be  
8 further considered for therapeutic purposes [127].

9  
10 Further in relation with the above-mentioned subversion of PrP<sup>C</sup>-mediated pathways by  
11 PrP<sup>Sc</sup> or A $\beta$ , the potential benefit of targeting Fyn with the small molecule inhibitor  
12 saracatinib is now being evaluated within a clinical trial focusing on AD [128]. In view of  
13 the central role exerted by Fyn in the recruitment of pathogenic cascades by prions [43],  
14 whether the same strategy may apply to TSEs seems worth investigating. Likewise,  
15 PDK1 overactivation was recently identified as another common feature of TSEs and AD,  
16 whose inhibition allows alleviating both diseases [107]. Of note, although further work  
17 is needed to develop inhibitory molecules devoid of intrinsic toxicity, treatment was  
18 shown to be effective while starting at a relatively late stage [107]. Besides, the  
19 observation that PDK1 overactivation in AD can be antagonized through silencing of  
20 PrP<sup>C</sup> [107] points to an interesting link between PrP<sup>C</sup> signalling and PDK1, which  
21 deserves further investigation.

22  
23 The group of Mallucci adopted a different approach based on targeting a generic  
24 pathway sustaining neurodegeneration. A commonality between TSEs, AD and  
25 Parkinson's disease is the impairment in the unfolded protein response (UPR) [129].  
26 One effector of this pathway is the eIF2 $\alpha$  elongation factor, whose phosphorylation halts  
27 protein synthesis. Following the demonstration that translational repression by  
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1 phosphorylated eIF2 $\alpha$  mediates prion neurodegeneration [130], Moreno et al.  
2 documented that inhibition of the UPR using an orally-administered pharmacological  
3 compound could abrogate the development of clinical disease in prion-infected mice,  
4 even when starting treatment after the emergence of behavioural signs [131]. Whether  
5 the advantage of this treatment is comparable to that afforded by others such as PDK1  
6 inhibition is unclear at present. In this respect, the development of standardized  
7 methods using defined mouse models and prion strains would help launch comparative  
8 studies to assess the relative benefit of various therapeutic approaches since the onset  
9 and progression of prion pathogenesis is highly synchronous in inoculated mice,  
10 contrary to AD mouse models. Notwithstanding, it is worthy to note that the  
11 suppression of eIF2 $\alpha$  phosphorylation was similarly shown to be beneficial in a mouse  
12 model of AD [132], suggesting that targeting the UPR may represent a powerful strategy  
13 to combat various neurodegenerative disorders [129]. Because transient  
14 phosphorylation of eIF2 $\alpha$  is involved in proteostasis, one important challenge for the  
15 next years would be to develop UPR-targeting therapeutic approaches that preserve the  
16 beneficial function of eIF2 $\alpha$ , as recently outlined [129]. Some progress towards this  
17 goal may be achieved through further delineating the link between PrP<sup>C</sup> signalling and  
18 eIF2 $\alpha$ , which has been but barely addressed until now [47].

19 Finally, an emerging axis focuses on the protective properties of the N1 PrP<sup>C</sup> fragment.  
20 Multiple studies have ascribed the neuroprotective role of PrP<sup>C</sup> to the N-terminal  
21 domain and have suggested that this action is, at least partly, supported by its soluble N1  
22 fragment [92, 133]. Recently, building upon the mapping of the binding sites of A $\beta$   
23 oligomers to the N-terminal region of PrP<sup>C</sup> (see Fig. 1), several groups have documented  
24 that soluble N1 is endowed with the capacity to trap A $\beta$  oligomers and thereby protect



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against A $\beta$ -induced neurotoxicity in various paradigms [25, 134-136]. The challenge now is to translate these observations into therapeutic strategies [137].

## **Conclusion**

The recent array of convergent data supporting the view that the subversion of PrP<sup>C</sup>-dependent signalling cascades is a pathogenic trigger in both prion and Alzheimer's diseases have sparked renewed interest on the physiological neuronal function exerted by PrP<sup>C</sup>. While considerable progress has been achieved in deciphering the signalling events instructed by PrP<sup>C</sup>, the challenge now is to reach a global view of the pathways orchestrated by PrP<sup>C</sup> according to the ligands at the play and the neuronal subtype considered, as well as their potential interconnections. Besides, further increasing our knowledge of PrP<sup>C</sup>-dependent signalling cascades may allow the identification of additional effectors, a subset of which may represent potential targets according to their status in disease. Overall, multiple strategies are now being exploited to counteract the toxic cascades arising from the deviation of PrP<sup>C</sup>-mediated signalling and we may hope some will reach success in the near future.

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We apologize to colleagues in the field whose work we were unable to cite owing to space limitations. We acknowledge financial support from the ANR, INSERM, as well as the Region Ile de France (DIM-Stem Pôle).

The authors declare no conflict of interest.

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**Table 1:**  
Downstream targets of PrP<sup>C</sup>-mediated signalling in a neuronal context (IEG: immediate early genes; SMase: sphingomyelinase)

<b>Targets</b>	<b>Cell type / tissue</b>	<b>Physiological response</b>	<b>Reference</b>
<b>Src kinases</b>			
<i>Fyn</i>	1C11-derived bioaminergic neuronal cells		[40]
	Primary hippocampal neurons	Neurite outgrowth	[29]
	PC12 neuronal cells	Neurite outgrowth	[41]
<i>Lyn</i>	1C11-derived serotonergic neuronal cells	Potentialiation of neurotransmitter release	[27]
	Raphe	Potentialiation of neurotransmitter release	[27]
<b>PI3K/Akt</b>			
<b>PKA</b>	N2a neuroblastoma cells	Cell survival	[46]
	Primary hippocampal neurons	Protein synthesis	[47]
	1C11-derived serotonergic neuronal cells	Potentialiation of neurotransmitter release	[27]
<b>PKA</b>	Rat retina	Neuroprotection	[49]
	Primary hippocampal neurons	Neuroprotection	[50]
	Hippocampal slices	Synaptic plasticity	[48]
<b>NADPH oxidase</b>			
<b>ERK1/2</b>	1C11-derived bioaminergic neuronal cells		[51]
	Rat retina	Neuroprotection	[49]
	SN56 cells		[52]
	Primary hippocampal neurons	Neurite outgrowth	[50]
	1C11-derived bioaminergic neuronal cells		[51]
<b>GSK3β</b>	Primary hippocampal neurons	Neurite outgrowth	[56]
	1C11-derived serotonergic neuronal cells	Potentialiation of neurotransmitter release	[27]
	Raphe	Potentialiation of neurotransmitter release	[27]
<b>TACE</b>			
<b>mTOR</b>	1C11-derived bioaminergic neuronal cells	Neurotransmitter catabolism	[53]
	Primary hippocampal neurons	Protein synthesis	[47]
<b>CREB</b>			
<b>SMase</b>	1C11-derived bioaminergic neuronal cells	Transcription of IEG	[54]
	Hippocampal cell lines, mouse brain		[55]
<b>Ca<sup>2+</sup></b>	Hippocampal neurons		[58]
	Primary hippocampal neurons	Neuroprotection, neuronal survival	[57]
	Primary hippocampal neurons	Neurite outgrowth	[56]
	Dorsal root ganglia neurons	Axonal growth	[59]

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**Table 2:**  
Functional interactions between PrP<sup>C</sup>-mediated signalling with neurotransmitter receptors in physiological or pathological contexts

Receptor	Cell type / tissue	Link with PrP <sup>C</sup> signalling	References
<b>Serotonergic</b>			
<i>5-HT1BR, 5-HT2AR, 5-HT2BR</i>	1C11-derived serotonergic neuronal cells	Modulation of couplings	[40]
<i>5-HT1BR</i>	1C11-derived serotonergic neuronal cells	Relocalization of receptor, blockade of activity	[27]
<b>Glutamatergic metabotropic</b>			
<i>mGlu1R, mGluR5</i>	Primary hippocampal neurons	LNγ1-induced neurite outgrowth	[56]
<i>mGlu5R</i>	Cortical neurons	Aβ-induced alteration of neuronal processes	[63]
<i>mGlu5R</i>	Hippocampus	Aβ-induced facilitation of LTD	[64]
<b>Glutamatergic ionotropic</b>			
<i>GluN2DR</i>	Hippocampal slices	Negative regulation	[66]
<i>GluN2BR</i>	Hippocampal slices	Internalization	[67]
<i>NMDAR</i>	SH-SY5Y cells	Aβ-induced neurotoxicity	[68]
<i>GluN2BR</i>	Cortical neurons	Aβ-induced Internalization	[44]
<i>NMDAR</i>	Hippocampal neurons	Aβ-induced neurotoxicity	[69]
<b>Cholinergic ionotropic</b>			
<i>α7nAChR</i>	Hippocampal neurons	Neuroprotection, neuronal survival	[57]

## Legends to figures

**Figure 1:** Secondary structure of mouse PrP<sup>C</sup>. The alpha-cleavage (green) occurs at position 111/112 and generates the N1 and C1 fragments. The beta-cleavage (red) occurs in the vicinity of octapeptide repeats, which bind copper ions, and generates the N2 and C2 fragments. PrP<sup>C</sup> can also be shed from the plasma membrane through the action of ADAM10. Two main binding sites have been mapped for A $\beta$  to the very N-terminus (AA 23–50) and near the alpha-cleavage site at amino acids 92–110. The protective factor STI-1 and the matrix protein laminin bind to PrP<sup>C</sup> at amino acids 113–128 and 173–182, respectively. The alpha helices ( $\alpha$ ) and beta sheets ( $\beta$ ) are indicated.

**Figure 2:** Summary of the signalling cascades mobilized by PrP<sup>C</sup> in response to the binding of STI-1 or laminin, as well as their biological outcomes. Responses to PrP<sup>C</sup>-dependent signalling include neuroprotection [49] / neuronal survival [57], protein synthesis [47], potentiation of neurotransmitter release [27], axonal growth [59] and neurite outgrowth [56].

**Figure 3:** Schematic representation of the corruption of PrP<sup>C</sup>-mediated signalling in prion and Alzheimer's diseases. PrP<sup>Sc</sup> accumulation and A $\beta$  oligomers promote the recruitment of various effectors of PrP<sup>C</sup>, including Fyn, NADPH oxidase and the MAP kinases ERK1/2. In the context of prion infection, it leads to a strong reduction in MMP-9 mRNAs and activity, which drives impairment in A $\beta$  clearance, causing A $\beta$  accumulation [43]. In Alzheimer's disease, the A $\beta$ -PrP<sup>C</sup>-Fyn cascade promotes Tau hyperphosphorylation [114] as well as impairment of the NMDA receptors surface localization [44]. PrP<sup>C</sup> is also involved in the deleterious A $\beta$ -dependent overactivation of PDK1 [107].

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Figure 1  
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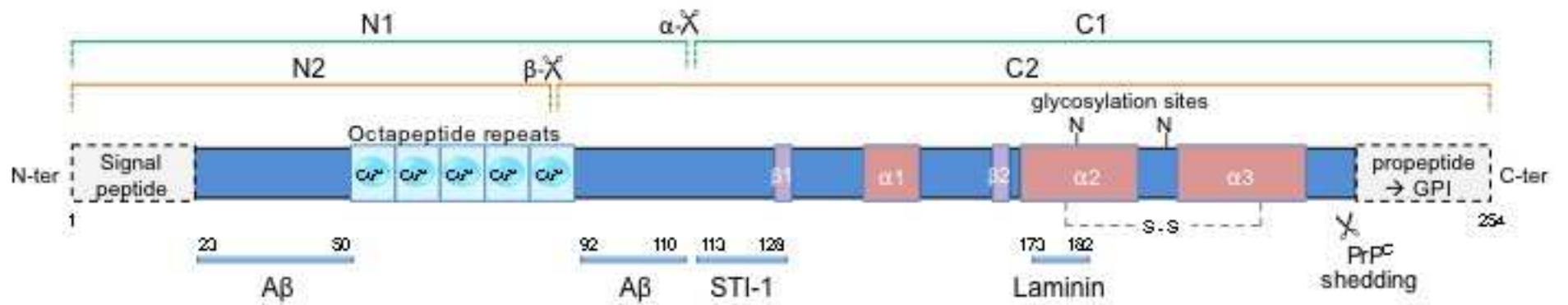


Figure 1

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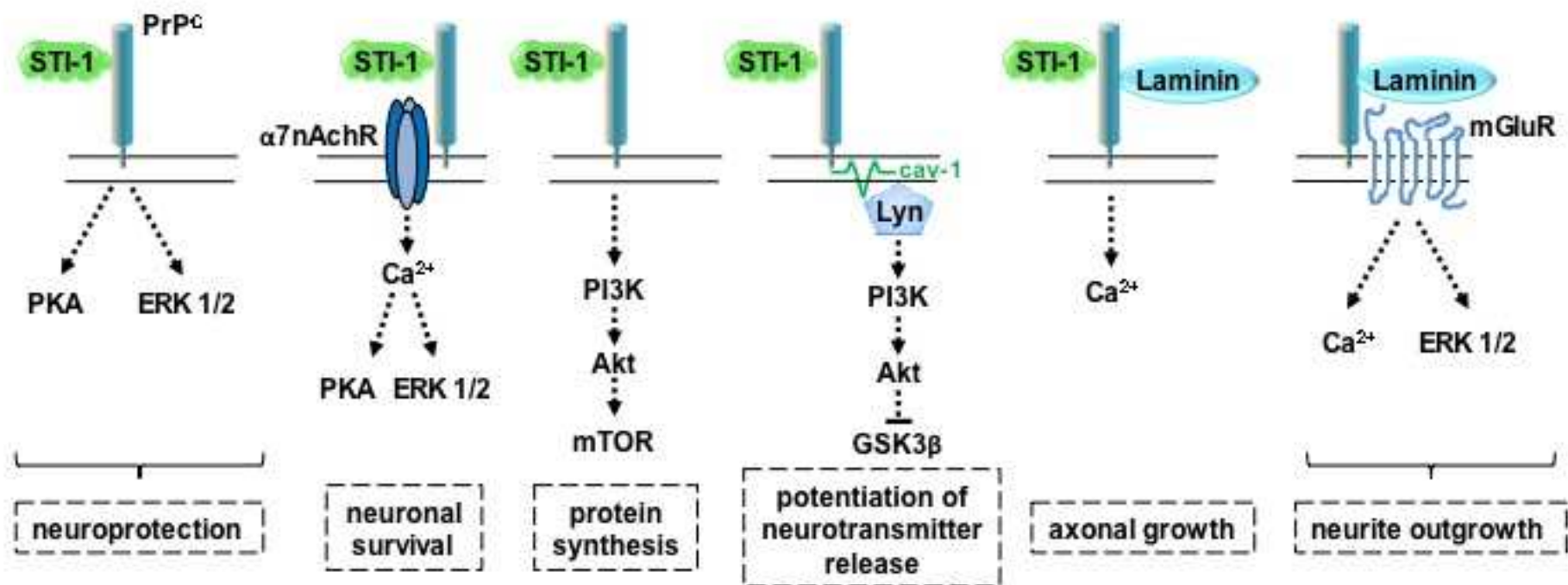


Figure 2

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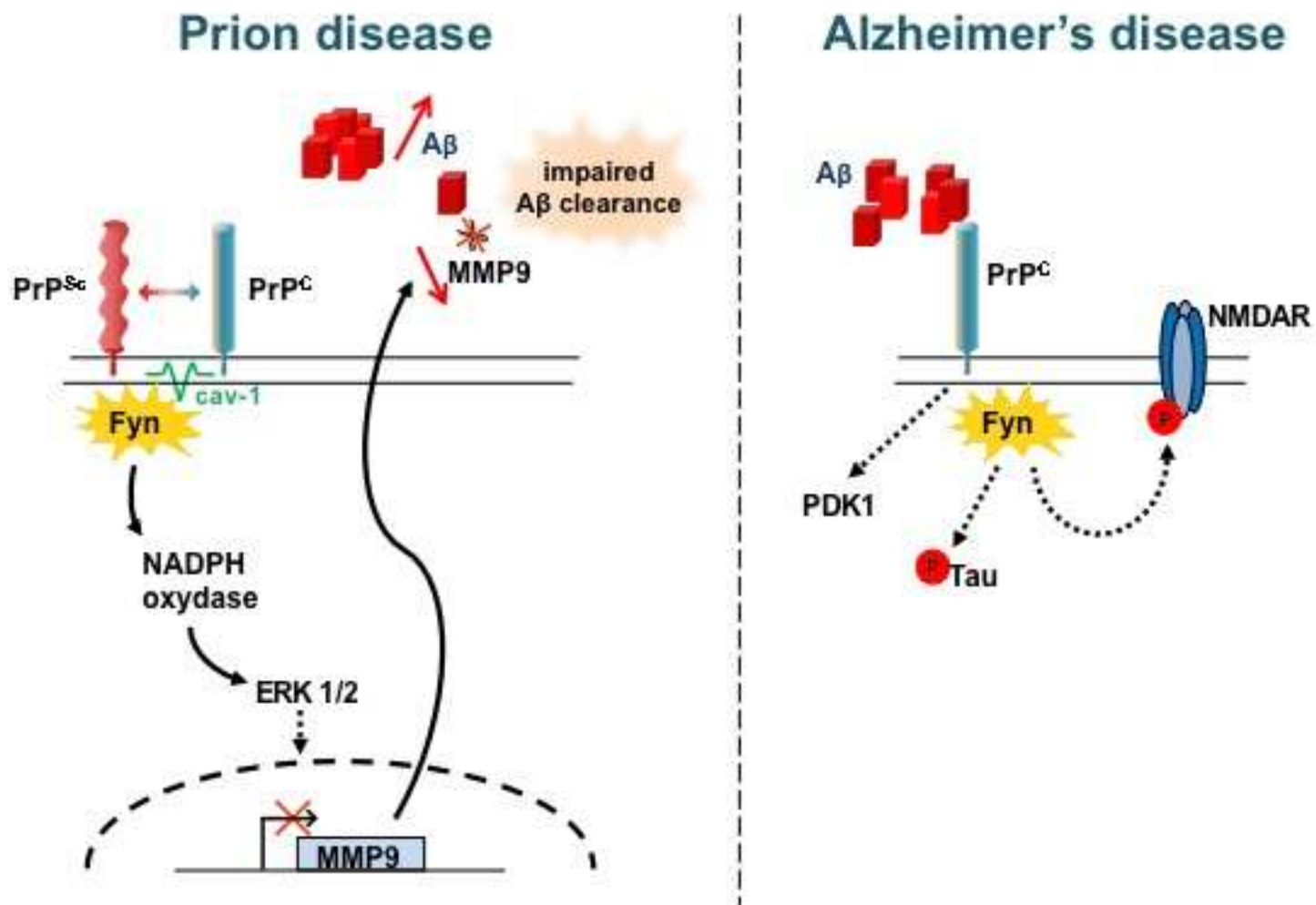


Figure 3