



# The cellular prion protein (PrP<sup>C</sup>) as neuronal receptor for $\alpha$ -synuclein

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**ABSTRACT.** The term ‘prion-like’ is used to define some misfolded protein species that propagate intercellularly, triggering protein aggregation in recipient cells. For cell binding, both direct plasma membrane interaction and membrane receptors have been described for particular amyloids. In this respect, emerging evidence demonstrates that several  $\beta$ -sheet enriched proteins can bind to the cellular prion protein (PrP<sup>C</sup>). Among other interactions, the physiological relevance of the binding between  $\beta$ -amyloid and PrP<sup>C</sup> has been a relevant focus of numerous studies. At the molecular level, published data point to the second charged cluster domain of the PrP<sup>C</sup> molecule as the relevant binding domain of the  $\beta$ -amyloid/PrP<sup>C</sup> interaction. In addition to  $\beta$ -amyloid, participation of PrP<sup>C</sup> in binding  $\alpha$ -synuclein, responsible for neurodegenerative synucleopathies, has been reported. Although results indicate relevant participation of PrP<sup>C</sup> in the spreading of  $\alpha$ -synuclein in living mice, the physiological relevance of the interaction remains elusive. In this comment, we focus our attention on summarizing current knowledge of PrP<sup>C</sup> as a receptor for amyloid proteins and its physiological significance, with particular focus on  $\alpha$ -synuclein.

**KEYWORDS.**  $\alpha$ -synuclein, charged cluster domain, interneuronal transport, LAG3, neurodegeneration, PrP<sup>C</sup>, Parkinson disease

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Parkinson's disease (PD) is the second most common neurodegenerative disease worldwide. Motor disabilities, globally called parkinsonism, are characteristic of the disorder; these may be preceded by neurovegetative symptoms, sleep disorders, and loss of olfaction; neurocognitive deficits may also appear with disease progression leading to dementia (i.e., Parkinson disease dementia, PDD). Histologically, PD is characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta, which is causative of parkinsonism, and the presence of intraneuronal insoluble inclusions called Lewy Bodies (LB) and Lewy Neurites (LN) in several brain regions.<sup>1</sup> LB/LN aggregates contain various misfolded proteins such as ubiquitin,<sup>2</sup> tau,<sup>3</sup> and lipids<sup>4</sup> but their major component is hyperphosphorylated  $\alpha$ -synuclein.<sup>5</sup> Abnormal  $\alpha$ -synuclein aggregates appear, in addition to PD, in various  $\alpha$ -synucleinopathies such as Dementia with Lewy Bodies (DLB) and multiple system atrophy (MSA).<sup>6</sup> In these disorders, aggregates are deposited in the brain in a filamentous form displaying a  $\beta$ -sheet structure<sup>7</sup> which is abnormally phosphorylated at Serine129 and is also ubiquitinated.<sup>8</sup> In addition, PDD, and particularly, DLB post-mortem brains often display accumulations of  $\beta$ -amyloid forming diffuse and neuritic plaques, and neurofibrillary tangles composed of abnormally hyperphosphorylated tau. In addition, the potential contribution of  $\alpha$ -synuclein to Alzheimer disease (AD) pathology is considered important today, with  $\approx 40\%$  of AD cases presenting LB/LN, often as amygdala-predominant Lewy body disease (LBD).<sup>9</sup>

### **'PRION-LIKE' PROTEINS AND NEURONAL SPREADING**

Most of the above-mentioned misfolded proteins (i.e.,  $\beta$ -amyloid, hyperphosphorylated tau, and abnormal  $\alpha$ -synuclein) are able to 'propagate' or 'spread' between cells in the same manner as infectious prions, a mechanism termed 'prion-like', 'prionoid', or simply 'prions' in several studies.<sup>10,11</sup> However, not

all the molecular properties of infective prions observed in transmissible spongiform encephalopathies (TSEs) have been demonstrated in these proteinaceous species.<sup>11</sup> The infectious spreading of pathogenic prions occurs between cells, tissues and, more relevantly, organisms. This is not described for all 'prion-like' molecules. As recently indicated by Harbi and Harrison in Prion,<sup>12</sup> 'prion-like activity' or 'prion-like propagation' may also refer to self-propagating protein aggregates that may not yet meet a stricter 'prion' definition. The term 'prion-like' for the 'propagative' activities of the misfolded proteins will be used in the present article. Moreover, in our review misfolded  $\alpha$ -synuclein protein becomes a 'prion-like' protein.

Although there is some disagreement, it is well established that the disease progression of some neurodegenerative disorders, such as AD and PD, seems to correlate with brain propagation of the misfolded protein between predictable anatomical pathways.<sup>13-17</sup> In PD and DLB, the sequential accumulation of  $\alpha$ -synuclein starts in the olfactory bulb, medulla oblongata, midbrain and forebrain, and neocortex.<sup>18</sup> Indeed, the spreading of pathological  $\alpha$ -synuclein is closely correlated with disease progression and is considered to be the underlying mechanism of progression of the disease.<sup>19</sup>

Extensive research has demonstrated that spreading of  $\alpha$ -synuclein can also be reproduced *in vivo* and *in vitro*. *In vivo*, peripheral (i.e.,<sup>20</sup>) or intracerebral injections of recombinant  $\alpha$ -synuclein protofibrils or insoluble fractions of  $\alpha$ -synuclein derived from affected brains trigger conversion of natural endogenous  $\alpha$ -synuclein into the abnormal misfolded form, and this misfolded  $\alpha$ -synuclein propagates in the brains of wild-type mice,<sup>6,21</sup>  $\alpha$ -synuclein transgenic mice,<sup>22,23</sup> monkeys,<sup>24</sup> and marmosets.<sup>25</sup> *In vitro* experiments, and more relevantly, the emerging development of 'lab-on-a-chip' device cultures based on microfluidics, have been of great value in helping to determine the cell-to-cell transport of several amyloids including  $\alpha$ -synuclein (i.e.,<sup>26-29</sup>). Thus, recombinant  $\alpha$ -synuclein fibrils<sup>27,28</sup> as well as LB extracts<sup>26</sup> can spread between neurons and astroglial cells growing in these devices.<sup>26</sup> Several mechanisms have been reported

for  $\alpha$ -synuclein spreading using these or other *in vitro* methods, such as extracellular vesicles and tunneling nanotubes (TNTs).<sup>13,30-35</sup> In addition to these descriptions, several groups have started to measure the presence of membrane receptors for  $\alpha$ -synuclein and/or other amyloids.

### **A CHARGED DOMAIN OF PRP<sup>C</sup> IS A COMMON 'DOCKING-DOMAIN' FOR SEVERAL 'PRION-LIKE' PROTEINACEOUS SPECIES**

Several studies have reported that  $\beta$ -sheet rich amyloid proteins (including  $\alpha$ -synuclein) can interact with plasma membrane (e.g.,<sup>36</sup>). Although this interaction might be involved in amyloid internalization leading to cytotoxicity, 'docking' and receptor-mediated interaction activities at plasma membrane might support most of the physiological activities of oligomeric proteinaceous species.<sup>37</sup> PrP<sup>C</sup> can bind with numerous membrane-associated molecules including adhesion molecules, growth-factor receptors, and neurotransmitter receptors, among others. More relevantly, PrP<sup>C</sup> has been described as a high-affinity binding partner of oligomeric  $\beta$ -amyloid (A $\beta$ )—a relevant finding in determining the early trigger in AD.<sup>38-43</sup> However, this interaction (A $\beta$ -PrP<sup>C</sup>) is not exclusive since other studies have determined that the N-terminal domain of PrP<sup>C</sup> can bind to several  $\beta$ -rich peptides, including A $\beta$ .<sup>44,45</sup> Indeed, mapping studies point to the  $\approx$  90–110 amino acids located in the second charged cluster of PrP<sup>C</sup> as the main residues responsible for A $\beta$  binding<sup>40,46</sup> (see<sup>47</sup> for a recent description of PrP<sup>C</sup> domains). Although interaction between PrP<sup>C</sup> and A $\beta$  has been demonstrated in several studies,<sup>38-43</sup> some observations indicate that PrP<sup>C</sup> is not a mediator of the neurotoxic effects of A $\beta$  (i.e.,<sup>48-51</sup>). Starting from these pioneering PrP<sup>C</sup>-A $\beta$  binding descriptions, several laboratories have started to analyze whether PrP<sup>C</sup> may also be a 'cellular partner' for other proteinaceous species displaying 'propagative' properties, and to determine whether PrP<sup>C</sup> participates in or regulates the spreading of these 'prion-like' proteins

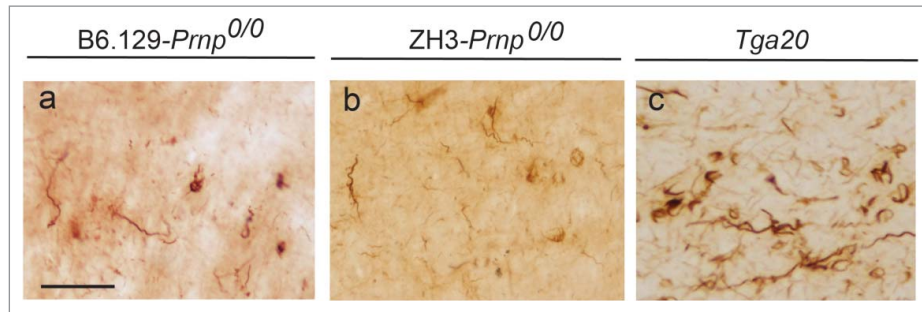
and their associated neuropathology. Results published recently by our group point out that, in addition to A $\beta$ , membrane-anchored PrP<sup>C</sup> can also bind to  $\alpha$ -synuclein fibers.<sup>27</sup>

Several receptors have been described as binding  $\alpha$ -synuclein. It has been shown that  $\alpha$ -synuclein binds to Na<sup>+</sup>/K<sup>+</sup>-ATPase subunit  $\alpha$ 3,<sup>52</sup> lymphocyte-activation gene 3 (LAG3),<sup>53</sup> neurexin,<sup>52,53</sup> amyloid  $\beta$  precursor-like protein 1 (APLP1),<sup>53</sup> and PrP<sup>C</sup>.<sup>27</sup> Although  $\alpha$ -synuclein is implicated in the binding, uptake, and/or trafficking of  $\alpha$ -synuclein protofibrils, some details of the process are missing, and for most of them except LAG3 and PrP<sup>C</sup>, their putative participation in the spreading of  $\alpha$ -synuclein and interneuronal transport has not been fully investigated. For LAG3 and PrP<sup>C</sup>, their binding and participation in  $\alpha$ -synuclein expansion has been analyzed *in vitro* and *in vivo*.<sup>27,53</sup> In both cases, the absence of the protein receptor (LAG3 or PrP<sup>C</sup>) largely decreases but does not fully impair  $\alpha$ -synuclein spreading *in vivo*.<sup>27,53</sup> Recent unpublished from our group noted that this decrease in  $\alpha$ -synuclein spreading in the absence of PrP<sup>C</sup> may occur in different strains of mice lacking functional PrP<sup>C</sup>, by avoiding an indirect effect of the 'Prnp-flanking genes' observed in the Zurich I (ZH1)-derived mice<sup>47,54,55</sup> (Fig. 1). Conversely, the overexpression of Prnp enhances  $\alpha$ -synuclein spreading and the generation of the phosphorylated form of  $\alpha$ -synuclein (p- $\alpha$ -synuclein) in anatomically connected regions (i.e., striatum  $\rightarrow$  motor cortex<sup>27</sup>) (Fig. 1c). These results were obtained using different Prnp genotypes, Prnp<sup>+/+</sup> and Prnp<sup>0/0</sup> (B6.129 (ZH1) Prnp<sup>0/0</sup><sup>27</sup> and Zurich 3 (ZH3) Prnp<sup>0/0</sup> mice<sup>54</sup>), and Tga20 (Prnp-overexpressing) mice under a B6.129 background<sup>27</sup> (Fig. 1).

### **TOWARD UNCOVERING OF THE PHYSIOLOGICAL RELEVANCE OF $\alpha$ -SYNUCLEIN-PRP<sup>C</sup> INTERACTION: LAST-MINUTE QUESTIONS**

Although the interaction between  $\alpha$ -synuclein and PrP<sup>C</sup> has been described, as has a

FIGURE 1. Increased p- $\alpha$ -synuclein aggregate labeling in the motor neocortex in *Tga20* mice compared with B6.129 (ZH1 *Prnp*<sup>0/0</sup>) and ZH3 *Prnp*<sup>0/0</sup> mice. Examples of p- $\alpha$ -synuclein aggregates in the cortex of B6.129 (ZH1) *Prnp*<sup>0/0</sup> (a); ZH3 *Prnp*<sup>0/0</sup> (b) and *Tga20* mice (c) injected with recombinant mouse  $\alpha$ -synuclein fibrils in the post-commissural striatum. Note the relevant accumulation of p- $\alpha$ -synuclein in intracellular deposits of retrograde labeled neurons in cortical layer V of *Tga20* mice. Scale bar: a = 100  $\mu$ m pertains to b and c.



correlation between *Prnp* expression and p- $\alpha$ -synuclein spreading *in vitro* and *in vivo*, new, challenging questions have emerged. Several open questions at both the cellular level and that of neurodegeneration warrant further study:

- i)  $\alpha$ -Synuclein can be transported intercellularly through several mechanisms. However, the participation of PrP<sup>C</sup> in  $\alpha$ -synuclein seeding properties and particular transport mechanisms needs further research.
- ii) Astroglial cells participate in  $\alpha$ -synuclein spreading.<sup>26</sup> Since PrP<sup>C</sup> is expressed in neurons and glial cells,<sup>56</sup> PrP<sup>C</sup> might also play a role in  $\alpha$ -synuclein glia-to-neuron transmission.
- iii) The putative participation of PrP<sup>C</sup> in the neurotoxic effects of  $\alpha$ -synuclein calls for further attention. Conversely, the actions of this binding in PrP<sup>C</sup> biology and physiology, both healthy and unhealthy, are still unknown.
- iv) The vast majority of PD patients are sporadic, but mutations in the *SNCA* gene encoding  $\alpha$ -synuclein A53T, A30P, E46K, A53E, H50Q, and G51D cause autosomal-dominant forms of PD.<sup>57</sup> As the  $\alpha$ -synuclein/PrP<sup>C</sup> interaction takes place in the second charged cluster of the PrP<sup>C</sup>, the question of whether these point

mutations may alter  $\alpha$ -synuclein/PrP<sup>C</sup> interaction needs to be addressed.

- v)  $\alpha$ -synuclein protofibrils bind to PrP<sup>C</sup> in their second charged cluster domain, sharing this binding motif with A $\beta$ . This suggests that the effort to block PrP<sup>C</sup>/A $\beta$  interaction with molecules (i.e., antibodies<sup>58</sup>) or chemical compounds could also be a potential therapeutic intervention for  $\alpha$ -synuclein spreading and, likely, for synucleopathies.

As Santiago Ramón y Cajal said “*Ideas do not last long. We must do something with them.*” We hope that the ideas discussed above will evolve very quickly through the use of newly emerging techniques (i.e, lab-on-a-chip, organoids, etc.) under the umbrella of new mutant mice to more fully reveal the role of PrP<sup>C</sup> in neurodegeneration.

#### **DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST**

No potential conflicts of interest were disclosed.

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