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The prion protein in neuroimmune crosstalk

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ABSTRACT

The cellular prion protein (PrP^C) is a medium-sized glycoprotein, attached to the cell surface by a glycosylphosphatidylinositol anchor. PrP^C is encoded by a single-copy gene, *PRNP*, which is abundantly expressed in the central nervous system and at lower levels in non-neuronal cells, including those of the immune system. Evidence from experimental knockout of *PRNP* in rodents, goats, and cattle and the occurrence of a nonsense mutation in goat that prevents synthesis of PrP^C, have shown that the molecule is non-essential for life. Indeed, no easily recognizable phenotypes are associate with a lack of PrP^C, except the potentially advantageous trait that animals without PrP^C cannot develop prion disease. This is because, in prion diseases, PrP^C converts to a pathogenic "scrapie" conformer, PrP^{Sc}, which aggregates and eventually induces neurodegeneration. In addition, endogenous neuronal PrP^C serves as a toxic receptor to mediate prion-induced neurotoxicity. Thus, PrP^C is an interesting target for treatment of prion diseases. Although loss of PrP^C has no discernable effect, alteration of its normal physiological function can have very harmful consequences. It is therefore important to understand cellular processes involving PrP^C, and research of this topic has advanced considerably in the past decade. Here, we summarize data that indicate the role of PrP^C in modulating immune signaling, with emphasis on neuroimmune crosstalk both under basal conditions and during inflammatory stress.

1. Background

1.1. Prion diseases

The prion protein is known for its pivotal role in prion diseases, such as Creutzfeldt-Jakobs disease in humans, bovine spongiform encephalopathy in cattle, and scrapie in small ruminants. Prion disease belong to a group of neurodegenerative disorders characterized by accumulation of pathogenic protein aggregates within and around neurons (Kovacs and Budka, 2008). Such brain proteinopathies include prevalent human diseases like Alzheimer's and Parkinson's diseases. Prion diseases may be inherited, sporadic or infectious, and, in accordance with the original "protein-only" hypothesis (Prusiner, 1982), animals that do not express PrP^C (*Prnp* knockout) do not replicate prions and are therefore resistant to prion diseases (Büeler et al., 1993; Prusiner et al., 1993). During prion disease, PrP^C levels decrease (Mays et al., 2014b) and physical interactions between endogenous PrP^C and pathogenic PrP^{Sc} conformers probably divert PrP^C away from its physiological partners. This may lead to a loss of function and, importantly, a potential gain in PrP^C-mediated toxic signaling with resultant neuronal death (Winklhofer et al., 2008). Clearly, corruption of the normal cellular function of PrP^C can have adverse effects on neuronal viability, highlighting the need for a better understanding of PrP^C physiology.

1.2. Biogenesis and structure of PrP^C

The prion protein gene, *PRNP*, encodes a 253 amino acid (aa) precursor protein with an endoplasmic reticulum (ER)-targeting sequence for translocation into the secretory route. During transit through the ER and Golgi apparatus, PrP^C is modified by two complex asparagine-linked sugar moieties, a disulfide bond, and a C-terminal glycosylphosphatidylinositol (GPI) anchor, localizing the protein to glycolipid-enriched membrane domains (Tatzelt and Winklhofer, 2004). NMR studies have shown that the N-terminal half of the protein, of about 100

Abbreviations: ADAM10, A disintegrin and metalloproteinase domain-containing protein 10; EAE, experimental autoimmune encephalomyelitis; TGF-β, transforming growth factor beta; TNF-α, tumor necrosis factor alpha; TNFR1, tumor necrosis factor receptor 1; TACE, tumor necrosis factor alpha converting enzyme; STI1, stress-inducible phosphoprotein 1; ISGs, type I interferon-stimulated genes; MHC, major histocompatibility complex; α7nAchR, α7 nicotinic acetylcholine receptor; Akt, protein kinase B; ERK, extracellular signaling-regulated kinase; STAT1, signal transducer and activator of transcription 1

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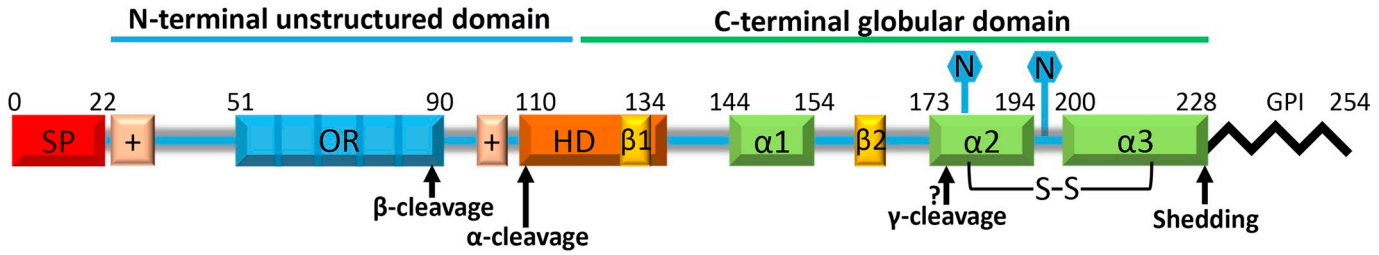

Fig. 1. Schematic overview of the mammalian prion protein structure and sites of processing. The signal peptide (SP) is removed in the endoplasmic reticulum. The unstructured N-terminal domain contains two positively charged motifs and the octapeptide repeat region (OR). A hydrophobic domain (HD) spans across the transition of the N- and C-terminal domains. The globular domain contains three α-helixes and two short β-strands. Processing sites are indicated by arrows.

aa, is unstructured, whereas the C-terminal half is a well-structured globular domain containing three α-helices and two short, antiparallel β-sheets (Donne et al., 1997; Lysek et al., 2005; Riek et al. 1996, 1997; Zahn et al., 2000) (Fig. 1). A range of proteins interact with the N-terminal flexible tail (Béland and Roucou, 2012), but the functional implications of these interactions have been identified for only a few molecules. Considering the evolution of PrP^C, it is interesting to note that the three-dimensional structure of the globular domain of human (aa 121–230), chicken (aa 121–225), turtle (aa 121–225), and frog (aa 90–222) PrP^C show extensive similarities, indicating conserved activity (Calzolai et al., 2005).

GPI-anchored PrP^C at the cell surface, is ideally placed for moving between membrane domains and for interacting with transmembrane signaling complexes (reviewed in Linden, 2017). Moreover, proteolytic cleavage can result in PrP^C and PrP^C-derived peptides being released to the inter-cellular space and interacting in immune signaling. PrP^C can also form dimers and give rise to cis- and trans- PrP^C interactions.

1.3. Towards a biological function of PrP^C

Soon after it had been discovered that PrP^{Sc} is derived from the host-encoded PrP^C, mice with genetic knockout (KO) of *Prnp* were generated. Surprisingly, the first two *Prnp* KO strains, Zürich I (ZrchI) and Edinburgh (Edbg), showed no developmental or other phenotypic disturbances (Büeler et al., 1992; Manson et al., 1994). However, further investigations of *Prnp*-ablated mice have revealed subtle phenotypic changes, indicating possible functions for PrP^C (Table 1). Not surprisingly, the majority of these are related to the central nervous system (CNS), where PrP^C is abundant. For instance, PrP^C has been suggested to regulate circadian rhythms (Tobler et al., 1996), participate in formation of memory (Coitinho et al., 2003), and protect neurons from different types of stress, such as infarction (Weise et al., 2004) or apoptosis (Zanata et al., 2002). Some of these findings have been influenced by the genetic backgrounds of the mouse strains used (reviewed in Wulf et al., 2017). However, a widespread, but clinically subtle, late-onset demyelination of the peripheral nervous system (PNS) has been discovered in mice without PrP^C. This phenotype, which was not identified for twenty years, has been reported from both ZrchI and Edbg mice (Bremer et al., 2010), and also in the more recent ZrchIII line (Küffer et al., 2016; Nuvolone et al., 2016). This makes it the best characterized pathology caused by loss of PrP^C function. Other proposed PrP^C functions apparently become evident under stressful conditions, such as inflammation. In this review, we discuss interactions between PrP^C and the immune system with emphasis on neuroimmune crosstalk. For recent reviews covering other aspects of PrP^C physiology, see (Castle and Gill, 2017; Wulf et al., 2017).

2. PrP^C and the immune system

The presence of PrP^C throughout the nervous system and other immune-privileged organs like testicles and ovaries, combined with its presence in most immune cells, makes it ideally placed for participating in neuroimmune communication. In a previous review, we proposed the idea that PrP^C could contribute to the broadly defined phenomenon of immunological quiescence (Bakkebø et al., 2015). Indeed, subtle phenotypes observed under basal conditions in *Prnp* KO mice suggest that functions of PrP^C in the immune system are modulatory and perhaps easier to identify during acute stress when there is activation of innate immune responses. Importantly, the presence of PrP^C in both the immune system and the nervous tissues is not only relevant for the normal function of these cells, but plays a crucial role in the uptake, peripheral propagation, and dissemination of prions during prion infection (Donaldson et al., 2016; McCulloch et al., 2011; McCutcheon et al., 2011).

2.1. PrP^C in blood immune cells

PrP^C is expressed in immune-privileged stem-cell niches of the hematopoietic bone marrow and has been shown to be important for stem-cell renewal under stressful conditions (Zhang et al., 2006). Generally, high levels of PrP^C are maintained in mononuclear cell precursors, but it is downregulated during maturation of granulocytic and erythroid cell lines (Dodelet and Cashman, 1998). In humans, monocytes, lymphocytes, mast cells, neutrophils, platelets, and red blood cells all express PrP^C, albeit at varying levels (Dürig et al., 2000; Haddon et al., 2009). Intriguingly, there appears to be species differences in PrP^C expression on blood cells (Barclay et al., 2002; Holada and Vostal, 2000). In sheep and goats, resting granulocytes are negative for PrP^C, whereas mononuclear cells, primarily lymphocytes and monocytes, are strongly positive (Dassanayake et al., 2012; Halliday et al., 2005; Herrmann et al., 2001; Reiten et al., 2015).

Early investigations showed that cell-surface levels of PrP^C are promptly upregulated when T cells are activated, and that genetic removal of *Prnp* or pharmacological blocking of PrP^C impaired T-cell proliferation (Bainbridge and Walker, 2005; Cashman et al., 1990; Mabbott et al., 1997). Similarly, PrP^C appeared to modulate cytokine production and proliferation of T cells induced by MHC-driven interactions with dendritic cells (Ballerini et al., 2006). Furthermore, silencing of PrP^C resulted in murine T cells being skewed towards pro-inflammatory phenotypes (Hu et al., 2010). Interestingly, T-cell proliferation rates in PrP^C-deficient goats (Reiten et al., 2015) and cattle (Richt et al., 2007) were similar between cells with and without PrP^C, demonstrating that a prominent role for PrP^C in T-cell activation is not uniform among mammalian species. PrP^C is also strongly upregulated in activated murine neutrophils in response to increased serum levels of TGF-β and glucocorticoids (Mariante et al., 2012). These molecules are reliant on the hypothalamic-pituitary-adrenal axis, which is activated by systemic inflammation. Another cell type with high PrP^C expression is mast cells (Haddon et al., 2009). Although PrP^C was not found to be obligatory for mast cell differentiation, it was rapidly shed from the cell surface upon activation, such as during mast cell-dependent allergic inflammation (Haddon et al., 2009). The functional implications of these findings remain to be clarified, but it can be speculated that release of PrP^C into the surroundings can contribute towards balancing

Table 1
Putative PrP^C functions.

Proposed PrP^C functions	Condition/test	Selected references
Neuroprotection/cytoprotection	Acute cerebral infarction	(Doeppner et al., 2015; Mitteregger et al., 2007; Shyu et al., 2005; Spudich et al., 2005; Steele et al., 2009; Weise et al., 2004).
	Induction of apoptosis	(Chiarini et al., 2002; Lopes et al., 2005; Zanata et al., 2002).
	Excitotoxicity	(Gasperini et al., 2015; Rambold et al., 2008)
	Genotoxic stress	(Bravard et al., 2015; Senator et al., 2004; Watt et al., 2007)
	Oxidative stress	(Anantharam et al., 2008; Bertuchi et al., 2012; Dupiereux et al., 2008)
	Inflammation	(Gourdain et al., 2012; Hu et al., 2010; Tsutsui et al., 2008)
	Infection	Nasu-Nishimura et al. (2008)
	Brain trauma	Hoshino et al. (2003)
Cellular differentiation	Neurite outgrowth in cultured cells	(Beraldo et al., 2011; Bribián et al., 2012; Llorens et al., 2013; Lopes et al., 2005; Loubet et al., 2012; Santuccione et al., 2005)
Neuronal excitability	Electrophysiological recordings and kainate-induced seizures	(Beraldo et al., 2010; Carulla et al., 2011; Colling et al., 1996; Khosravani et al., 2008; Mallucci et al., 2002)
Modulation of circadian rhythms and sleep patterns	Sleep deprivation	(Huber et al., 1999; Sánchez-Alavez et al., 2007; Tobler et al., 1996)
Behavior (locomotor activity, anxiety, nest-building behavior, aggression, and depressive-like behavior)	E.g., exploration of unfamiliar environment, electric foot shock, forced swimming, and tail-suspension test	(Büdefeld et al., 2014; Coitinho et al., 2003; Gadotti et al., 2012; Lobão-Soares et al., 2007; Nico et al., 2005; Rial et al., 2009; Roesler et al., 1999; Schmitz et al., 2014)
Cognitive performance and memory	E.g., inhibitory avoidance task, Barnes circular maze test, and fear conditioning	(Coitinho et al., 2003; Criado et al., 2005; Manson et al., 1995; Schmitz et al., 2014)
Homeostasis of metals (copper, zinc, and iron)	E.g., chromatography and co-immunoprecipitation	(Gasperini et al., 2015; Hornshaw et al., 1995; Singh et al., 2009; Watt et al., 2012)
Myelin maintenance (PNS)	Histopathology, electrophysiology, hot-plate test, grip-strength test, and rotarod performance test	(Bremer et al., 2010; Küffer et al., 2016; Nuvolone et al., 2016)
Mediate neurotoxic effects of other molecules	Scrapie prions (Prion diseases)	(Brandner et al., 1996; Chesebro et al., 2005; Mallucci et al., 2003; Rambold et al., 2008)
	Amyloid beta (Alzheimer's disease)	(Lauren et al., 2009; Purro et al., 2018; Resenberger et al., 2011)
	α-synuclein (Parkinson's disease)	Ferreira et al. (2017)

inflammatory signaling in paracrine fashion. Of importance, a sub-type of mast cells resides on the brain side of the blood-brain barrier and communicates with neurons, astrocytes, and microglia (Dong et al., 2014). Thus, upon activation, mast cells act as first responders to initiate, amplify, and prolong immune and nervous responses.

Another key element of immune responses and neuroimmune crosstalk is tissue invasion by activated blood leukocytes. Several studies have shown that PrP^C modulates leukocyte extravasation (de Almeida et al., 2005; Linden et al., 2008; Liu et al., 2014) including into the CNS (Tsutsui et al., 2008). A possible way by which PrP^C can influence leukocyte migration is through interaction with adhesion molecules like β1 integrin (Richardson et al., 2015), which is a co-receptor for PrP^C (Loubet et al., 2012). Alternatively, the reported differences could reflect increased levels of chemoattractants and cytokines in PrP^C-deficient animals, rather than a direct effect of PrP^C in leukocyte adhesion. Again, contradictory findings have been reported in other animal models, in which similar tissue recruitment of leukocytes was observed independent of PrP^C expression (Gourdain et al., 2012; Salvesen et al., 2017a). Therefore, replication of murine studies on T-cell activation and leukocyte migration in the more recently developed co-isogenic *Prnp* KO lines could provide useful results.

2.2. PrP^C in neuroinflammation

One frequently used approach to study multiple sclerosis-like neuroinflammation is induction of experimental autoimmune encephalomyelitis (EAE) by injection of myelin oligodendrocyte glycoprotein. EAE is a complex condition accompanied by aggressive brain inflammation, demyelination, axonal loss, and gliosis (Constantinescu et al., 2011). Studies of EAE in *Prnp* KO mice have shown that loss of PrP^C exacerbates disease progression, with increased clinical severity and neuropathology, as well as higher transcription levels of pro-inflammatory cytokines, TNF-α and interleukin-1β, in comparison to that of PrP^C-expressing wild-types (Gourdain et al., 2012; Hu et al., 2010; Tsutsui et al., 2008). Mice overexpressing PrP^C displayed a further reduction in neuroinflammation, suggesting that PrP^C has neuroprotective functions during EAE *in vivo* (Hu et al., 2010). The greater severity of EAE in *Prnp* KO mice was initially linked to increased pro-inflammatory signaling by PrP^C-negative T cells (Hu et al., 2010), but a subsequent study suggested that neuronal lack of PrP^C could play an important role as well (Gourdain et al., 2012). Interestingly, PrP^C was co-immunoprecipitated with the Zeta chain-associated protein kinase 70 (ZAP-70), which is a key component of the T cell-receptor complex (Mattei et al., 2004). Moreover, reduced phosphorylation of ZAP-70 was observed in the presence of PrP^C, providing evidence for a functional role for PrP^C in dampening T-cell signaling (Hu et al., 2010). Notably, PrP^C has also been shown to have protective roles during inflammatory challenge in peripheral tissues, such as the spleen (Liu et al., 2014) and colon (Martin et al., 2011).

Despite these various observations suggesting that PrP^C plays a significant immunomodulatory role, particularly during inflammatory stress, the signaling pathways and molecular contexts involving PrP^C are still largely unresolved. Some advances in our understanding have, however, been made in recent years. Ezpeleta and colleagues showed that PrP^C could protect against TNF-α –mediated inflammation by stimulating cleavage of TFNR1, with subsequent release of soluble TNFR1 via the TACE α -secretase pathway, thus downregulating TNF-α signaling (Ezpeleta et al., 2017). TNF-α –mediated signaling has also been shown to regulate PrP^C levels on brain microvascular endothelial cells (BMVEC), an important component of the blood-brain barrier (Megra et al., 2018). Furthermore, knockdown of PrP^C in BMVEC caused increased permeability of the blood-brain barrier, which is a significant event of neuroinflammation. These mechanisms may, at least partly, explain observations of increased TNF-α-driven inflammatory pathology in *Prnp* KO animals. Interestingly, studies of human melanoma and adenocarcinoma cells expressing an immature and incompletely processed form of PrP^C, lacking its GPI anchor, have revealed that this non-functional PrP^C species enhances pro-inflammatory TNF-α signaling (Wu et al., 2017). Accordingly, genetic removal of pro-PrP in these cells reduced inflammatory signaling.

Studies of experimental acute cerebral infarction have shown that mice without PrP^C suffer larger infarction volumes than wild-type

controls. This has been considered to be partly due to increased signaling and activation of ERK1/2, STAT1, and pro-apoptotic caspase-3 pathways in the absence of PrP^C (Shyu et al., 2005; Spudich et al., 2005; Steele et al., 2009; Weise et al., 2004). Correspondingly, reduced activation of the PI3K-Akt pathway, which is a negative regulator of caspase-3 signaling, was observed in *Prnp* KO animals (Weise et al., 2006). Indeed, caspase 3 is a crucial mediator of neuronal apoptosis (Yang et al., 2002) and animals overexpressing PrP^C had smaller infarction sizes and reduced post-ischemic ERK1/2 activation (Shyu et al., 2005; Weise et al., 2008). Subsequently, interactions between stress-inducible phosphoprotein-1 (STI1), a co-chaperone released by astrocytes (Hajj et al., 2013), and PrP^C have been ascribed protective functions against ischemia-derived pathology (Beraldo et al., 2013; Zanata et al., 2002). Both PrP^C and STI1 are upregulated in the periphery of ischemic brains lesions of humans and rodents (Beraldo et al., 2013; Weise et al., 2004), and the STI1/PrP^C-interaction seemed to increase influx of bone marrow-derived cells into ischemic brain regions, thus triggering a self-protective mechanism to facilitate recovery after brain infarction (Lee et al., 2013). Recently, neuroprotection by PrP^C/STI1-signaling was shown to involve α7nAchR, in addition to activation of the neuronal activating A receptor, by increased levels of STI1 (Beraldo et al., 2018). Notably, ischemic stroke comprises both an acute and prolonged inflammatory response (Jin et al., 2010), and it is reasonable to assume the above-mentioned signaling overlaps with immunomodulatory signaling by PrP^C.

At the cellular level, neuroimmune crosstalk is maintained through an integrative network of neurons, microglia, astrocytes, and infiltrating immune cells, such as T cells (Tian et al., 2012) (Fig. 2). Importantly, all the cellular participants of neuroimmune crosstalk express PrP^C (Adle-Biassette et al., 2006; Bertuchi et al., 2012; Moser et al., 1995). A hallmark of acute neuroinflammation is activation of resident microglia, which participate in the phagocytosis of microbes or debris, as well as release of cytokines (Colonna and Butovsky, 2017). Early studies (Brown et al., 1998) using the immortalized murine microglia-like cell line BV2 indicated roles for PrP^C in cellular activation and survival (Shi et al., 2013), also following infection with *Mycobacterium bovis* (Ding et al., 2013). However, a further study using primary microglia failed to detect any effects of PrP^C on cell morphology, microglial markers, phagocytosis rate, or cytokine production, even following activation (Pinheiro et al., 2015). The authors of the latter study suggest that caution should be used in interpreting results from BV2 immortalized-cell lines alone in studying PrP^C function, as BV2 cells and primary microglia cultures differ in migration and cytokine production (Horvath et al., 2008). Astrocytes also play significant roles in brain inflammation, producing both pro- and anti-inflammatory chemokines (Kim et al., 2010). Astrocyte end-feet encircle endothelial cells at the blood-brain barrier and enable close proximity to systemic circulation and immune cells that infiltrate the perivascular space (Rungta and Charpak, 2016). Although the subject of few studies, astrocyte PrP^C seems to be important for the survival and differentiation of both astrocytes (Arantes et al., 2009) and neurons (Lima et al., 2007; Lopes et al., 2005). Interestingly, astrocytes overexpressing PrP^C showed higher levels of GFAP (Hartmann et al., 2013), a general marker of astrocyte activation and neuroinflammation. PrP^C also protected astrocytes from oxidative stress (Bertuchi et al., 2012), which could be important during inflammation caused by infarctions.

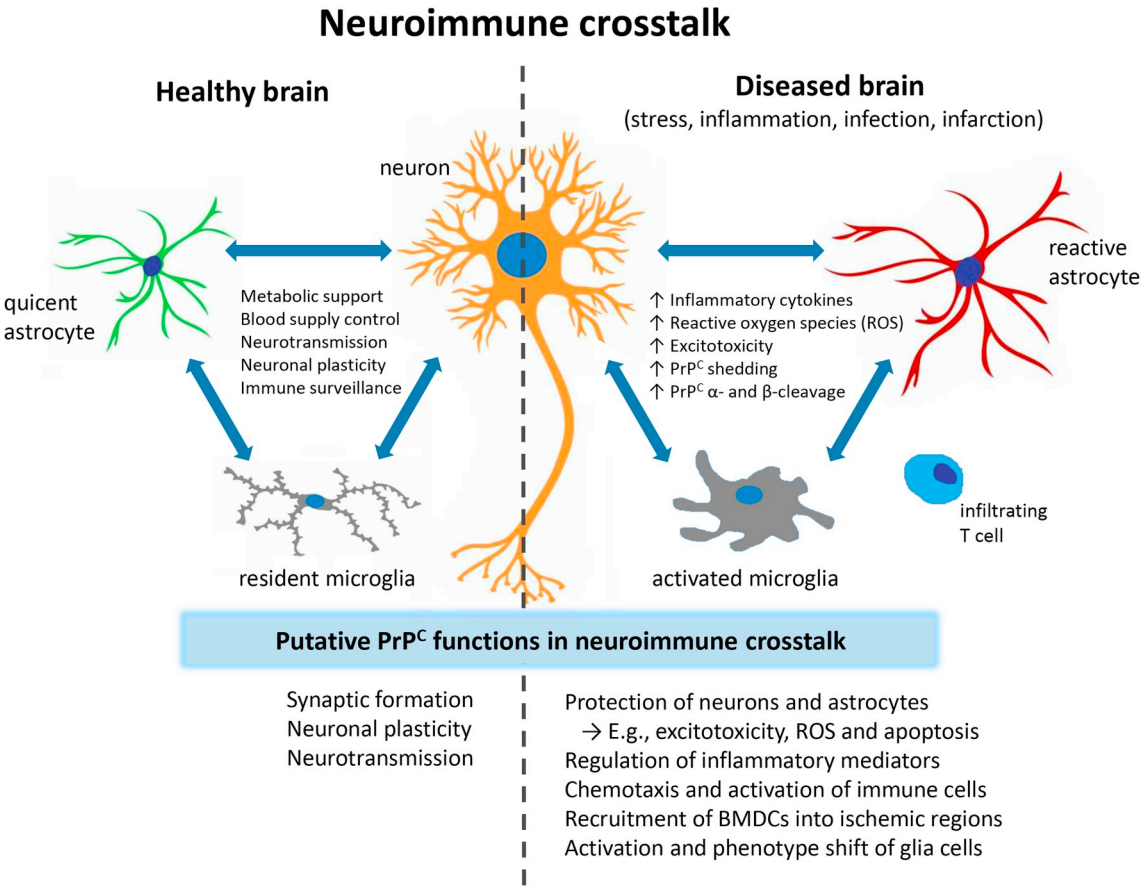

Fig. 2. Schematic overview of neuroimmune crosstalk between neurons, microglia and astrocytes in the CNS under normal (left) and pathological conditions (right). Resident astrocytes and microglia participate in maintaining homeostasis and neuronal activity under physiological conditions. Different pathological conditions may lead to disruption of this homeostasis and escalate into neuronal damage trough inflammation. Putative functions of PrP^C in regulating neuroimmune crosstalk at rest and during inflammation are indicated. Modified with permission from (Bi et al., 2013; Tian et al., 2012) distributed under a Creative Commons License (CC License).

Nevertheless, mechanistic evidence of how astrocyte PrP^C may modulate inflammation has not been clarified.

Taken together, these studies share the concept that PrP^C protects against neuroinflammation, probably by modulating the effects of cytokines and other inflammatory molecules, and thereby limiting tissue damage. Nevertheless, discrepancies between studies highlights the importance of cross-validating data using different model systems and experimental setups. For example, several studies reported that PrP^C regulates phagocytosis in macrophages (de Almeida et al., 2005; Uraki et al., 2010; Wang et al., 2014), but polymorphisms in a closely linked locus encoding *Sirpa* were later reported to have confounded these results (Nuvolone et al., 2013). Importantly, *Sirpa* participate in regulating other immune mechanisms as well (reviewed in van Beek et al., 2005), several of which overlap with proposed PrP^C functions. These include production of inflammatory cytokines (Smith et al., 2003), activation of T and dendritic cells (Latour et al., 2001), and trans-endothelial migration of neutrophils (Cooper et al., 1995) and monocytes (de Vries et al., 2002). Therefore, the use of loss-of-function phenotypes alone to address PrP^C function should be done with caution.

2.3. Proteolytic processing of PrP^C: signaling by PrP^C fragments

Mature PrP^C can be subject to proteolytic processing (Harris et al., 1993; Stahl et al., 1990). Soluble full-length PrP^C can be released from the cell membrane through the action of ADAM10 (Altmeppen et al., 2011). Furthermore, PrP^C can be cleaved by an unidentified protease at around aa 110 (α-cleavage), generating a soluble N1 fragment and a GPI-anchored C1 fragment containing the structured domain (Altmeppen et al., 2013; Chen et al., 1995; Mange et al., 2004; Mays et al., 2014a). Under stressful conditions with high levels of reactive oxygen species, a further cleavage of PrP^C has been observed (β-cleavage), which occurs about 20 aa N-terminal to the α-cleavage and releases the N2 fragment (Chen et al., 1995; Mange et al., 2004; McMahon et al., 2001). Thus, PrP^C-derived peptides are released to the inter-cellular space and may operate as signaling molecules in paracrine and autocrine fashion, as illustrated (Fig. 3). For a detailed review of PrP^C cleavage products and their putative physiological roles, see (Linsenmeier et al., 2017).

The cellular localization in which PrP^C or PrP^C fragments exert a (patho)physiological function is continuously under investigation. It has been confirmed that the N1 fragment binds a cell-surface receptor on Schwann cells and promotes myelin homeostasis (Küffer et al., 2016). Since a broad spectrum of proteins interacts with the N-terminal domain of PrP^C (reviewed in Béland and Roucou, 2012), *trans* signaling by N1 as a component of the immune response is also feasible. Indeed, neuroprotective functions originally linked to full length PrP^C may be attributed to both N1 and N2 fragments (Guillot-Sestier et al., 2009; Haigh et al., 2009; Mitteregger et al., 2007). In addition to binding to cell-surface receptors, it is also plausible that the N1 fragment can interact with nearby cells and/or enter cells to reach intracellular compartments. Importantly, the polybasic motif in the N-terminal domains of PrP^C (K^{23}KRPK) resembles the trans-activating transcriptional activator peptide from human immunodeficiency virus 1, and therefore has cell-penetrating activity (Lundberg et al., 2002; Wadia et al., 2008). Thus, N1 may enter the cell and interact with cytosolic components after it is liberated from GPI-anchored PrP^C. The N-terminal part of PrP^C has nucleic acid-binding properties with affinity for both DNA and RNA (Murdoch et al., 1990; Sklaviadis et al., 1993) and may adopt chaperon-like roles, resembling retroviral nucleocapsid proteins (Gabus et al., 2001; Manuelidis et al., 1995). Further roles for PrP^C- derived fragments, most notably N1, in the cellular household of cytoplasmic nucleic acids is an intriguing topic for further exploration, directly linked to basal (tonic) innate immunity signaling and putative effects on gene expression.

It has been shown that chronic lymphocytic inflammation with activated B cells and stromal follicular dendritic cells leads to focal up-regulation of PrP^C, and that such inflammatory loci can sustain prion replication in otherwise prion-free organs (Heikenwalder et al., 2005). As full-length PrP^C can be shed from immune cells (Haddon et al., 2009; Parizek et al., 2001), particularly during inflammation, several investigators have explored signaling effects of shed PrP^C on various immune cell populations. One way of expressing a secreted variant of PrP^C is by fusing PrP^C devoid of the GPI anchor or PrP^C fragments to the Fc portion of IgG1 (Krebs et al., 2006). Exposing immune cells to chimeric PrP-Fc proteins resulted in stimulation of ERK and Akt signaling. Activation seemed dependent upon the N-terminal tail of PrP^C, since similar constructs carrying the C-terminal part of PrP^C failed to bind (Krebs et al., 2006). The true physiological relevance of this and similar studies (Jeon et al., 2013; Seong et al., 2015) remains to be established. In transgenic mice, a secreted artificial PrP-immunoglobulin Fc (PrP-Fc_2) fusion protein that forms disulfide bond-stabilized dimers was not converted into PrP^{Sc} and delayed onset of prion disease (Meier et al., 2003). Interestingly, transgenic mice overexpressing a secreted variant of PrP^C devoid of the C-terminal GPI signal sequence (PrPΔGPI),

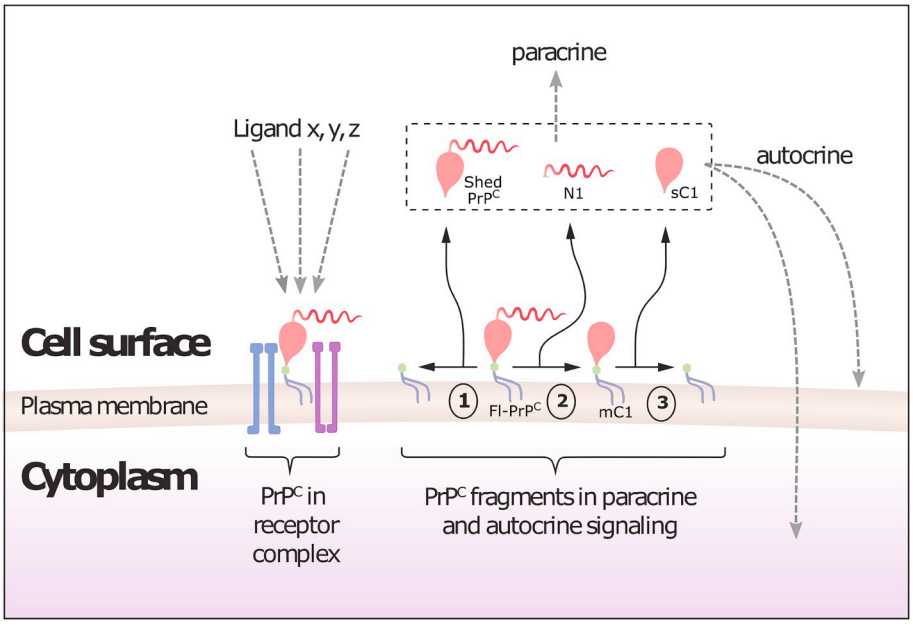

Fig. 3. Signaling by cell surface PrP^C and PrP^C fragments. Mature full-length PrP^C (Fl-PrP^C) is attached to the cell membrane through its GPI-anchor. Ligands can bind PrP^C which probably is associated with transmembrane co-receptors to initiate signaling into the cell. Shedding of PrP^C can be performed in close proximity to the GPI-anchor releasing soluble PrP^C into the extracellular space (1). The N-terminal domain (N1 fragment) can be released by α-cleavage leaving membrane bound C1 (mC1) attached to the cell surface (2). Finally, the C1 fragment can be shed form the cell surface in a soluble form sC1 (3). The released PrP^C fragments can probably mediate both intercellular communication (paracrine) and autocrine signaling.

spontaneously develop neurodegenerative prion disease with striking similarities to a sub-set of Gerstmann–Sträussler–Scheinker disease (Stöhr et al., 2011). This demonstrates that secreted PrP^C can be amyloidogenic and potentially harmful, suggesting that shedding of full-length PrP^C, at least in the brain, must be a tightly controlled process.

3. PrP^C-deficient goats: a spontaneous animal model to study immune signaling by PrP^C

3.1. Norwegian dairy goats naturally devoid of PrP^C

In 2012, a nonsense mutation in codon 32 in the *PRNP* gene of Norwegian dairy goats was discovered (Benestad et al., 2012). Animals homozygous for this mutation ($PRNP^{Ter/Ter}$) do not have PrP^C, and their *PRNP* mRNA levels are strongly reduced (Reiten et al., 2015; Salvesen et al., 2017a), probably through nonsense-mediated mRNA decay mechanisms. In a genetic survey of 1984 goat bucks in Norway, 216 (10.9%) animals carried the mutation, of which 13 (0.7%) were homozygous (unpublished results). Since its discovery, we have carried out a series of investigations of this unexpected, and apparently unique, non-transgenic "PrP^C knockout" model. New phenotypes could shed light on PrP^C physiology and cross-validate studies primarily carried out in inbred transgenic mouse models. Drawbacks to studies using this goat line are their outbred nature, with high individual variation, their slow reproductive capacity, and the high costs associated with housing and maintenance of the animals. However, goats have a longer life-expectancy than laboratory rodents and are natural hosts for prion disease. In addition, they are housed under standard goat husbandry conditions, with normal development of the intestinal gut flora and immune system, including responsiveness to vaccines. This is in contrast to the specific pathogen free (SPF) facilities used in housing laboratory rodents; such abnormally hygienic environments can profoundly impact the cellular composition of the innate and adaptive immune system (Beura et al., 2016), such that the immunomodulatory roles of PrP^C may be masked or camouflaged, and results obtained may be misleading. Goat kids raised in a goat herd are also required to develop social and behavioral characteristics according to flock standards, set by adult dominant females; although more than 50 animals without PrP^C have been bred and raised in our goat-herd facilities, we have not observed any behavioral abnormalities, such as anxiety or hyper-sensitivity towards triggers such as noise. However, detailed behavioral analyses have not yet been performed.

3.2. Subtle, but striking, phenotypes in PrP^C-deficient goats

An initial assessment of clinical, hematological, and immunological parameters of goats without PrP^C, revealed that animals without PrP^C had higher red blood cell counts, with slightly reduced cell volumes, than normal goats. The difference was subtle and clinically insignificant, but closer analyses reveled a gene-dose effect, with heterozygous animals showing an intermediate shift of the hematological profile (Reiten et al., 2015). This is strikingly similar to that observed in cattle with genetic ablation of *PRNP*, in which a virtually identical phenotype was noted (Richt et al., 2007). Thus, in two ruminant species, with obviously different genetic backgrounds, loss of PrP^C induced hematological alterations. In both species, this probably reflects an influence of PrP^C in bone marrow hematological stem-cell niches. Morphological analysis of bone marrow in goats without PrP^C did not reveal any obvious alterations, but further investigations on this topic, including the use of co-isogenic transgenic mice, should be considered. Analysis of monocyte phagocytic capacity *in vitro* showed that cells performed similarly, regardless of PrP^C status (Reiten et al., 2015). These observations suggest, as pointed out by Nuvolone and co-workers (Nuvolone et al., 2013), that some of the previously reported phenotypes may have been skewed by flanking genes, like *Sirpa*. Nevertheless, altered phagocytic ability has also been described in bone marrow-derived $Prnp^{0/0}$ macrophages infected with *Escherichia coli* (Wang et al., 2014). Since *E. coli* do not express CD47, which is the main ligand for SIRPα, the authors attributed their findings mainly to PrP^C. Thus, further studies are required to clarify the relationship between PrP^C and other molecules important for phagocytosis.

Based on the knowledge that goat peripheral blood mononuclear cells (PBMCs) have robust cell-surface PrP^C expression, a transcriptomic analysis of PBMCs was carried out (Malachin et al., 2017). In accordance with expectations and data from mice, only a minute fraction of genes was differentially expressed between the genotypes. However, in the absence of PrP^C, a mild increase in basal expression of type I interferon-stimulated genes (ISGs) was dominant (Malachin et al., 2017). This unexpected observation suggests that, at some currently unidentified level, PrP^C, influences resting-state innate immunity signaling. Cellular regulation of basal expression levels of ISGs is complex and multilayered, including crosstalk with gut microbiota and epigenetic mechanisms (reviewed in Ivashkiv and Donlin, 2014). Given the extreme sensitivity of ISGs to interferon stimuli, even a mild sub-clinical infection could underlie expression differences between animals (Lathe and Darlix, 2017). However, our initial study included eight age-matched clinically healthy animals of each genotype from the same flock at the same time-point, and therefore it is unlikely that one of the groups should selectively carry a sub-clinical viral infection. Moreover, subsequent studies of further groups of goats, of different ages and housed under different conditions, have shown the same gene expression difference between the groups (Salvesen et al. 2017a, 2017b).

In an experiment with acute inflammation caused by intravenous injection of *E.coli*-derived lipopolysaccharide (LPS), goats without PrP^C displayed significantly prolonged sickness behavior, dominated by depression and lack of interest in the surroundings (Salvesen et al., 2017a). Expression levels of the primary inducers of sickness behavior, IL-1β and TNF-α, were not altered in the brain at the time of euthanasia, but a transient increase almost immediately after LPS challenge is likely (Marques et al., 2009). As described previously, higher levels of these cytokines have been described in a range of *Prnp* KO models (Liu et al., 2014; Martin et al., 2011; Tsutsui et al., 2008), and could potentially contribute to the prolonged sickness behavior in goats. Although reports of LPS-induced sickness behavior in *Prnp*-ablated mice are lacking, a depressive-like behavior during standardized stress tests has been described (Gadotti et al., 2012). The profound sickness behavior in PrP^C-deficient goats corresponded with higher body temperatures over a prolonged period after LPS injection. Gene expression profiling of the hippocampus and choroid plexus (part of the blood-brain barrier) showed that PrP^C-deficient goats had a relatively stronger increase in expression levels of ISGs, but the opposite was the case for genes that are predominantly regulated by type II interferon (Salvesen et al., 2017a). Morphological analysis and activation scores for microglia and astrocytes appeared similar between the genotypes in both tissues. Further analysis of lung parenchyma, which is severely affected by LPS challenge, showed that goats without PrP^C had higher expression levels of genes downstream from inflammatory regulators like TNF-α, IL-1β and INF-γ (Salvesen et al., 2017b). Taken together, the results obtained from PrP^C-deficient goats accompany *Prnp* KO models in mice, and suggest that PrP^C can modulate immune responses (Table 2).

4. Conclusions and future perspectives

Following recognition of the role of PrP^{Sc} in prion diseases, significant efforts have been directed towards improving our understanding the physiological function of cellular PrP. In summarizing data derived primarily from transgenic mice without PrP^C, but also from observations in goats lacking this protein, it is clear that multiple lines of evidence indicate immunomodulatory roles for PrP^C. Firstly, PrP^C appears to convey cellular protection against inflammatory damage in a wide variety of experimental settings. Secondly, animals without PrP^C display immediate effects in terms of sickness behavior, demonstrating

Table 2
Summary of immune-related phenotypes in animals devoid of PrP.

Condition/test	$Prnp^{0/0}$ phenotypes	References
Experimental autoimmune encephalitis	Increased clinical severity Augmented neuropathology Increased pro-inflammatory signaling	(Gourdain et al., 2012; Hu et al., 2010; Tsutsui et al., 2008)
Encephalomycarditis infection	Suppressed microglial response Reduced leukocyte infiltration Increased neuronal apoptosis	Nasu-Nishimura et al. (2008)
Acute cerebral infarction	Larger infarction volumes Increased activation of ERK1/2 and STAT1	(Mitteregger et al., 2007; Shyu et al., 2005; Spudich et al., 2005; Weise et al., 2004).
Intracerebroventricular TNFα challenge	Increased neuroinflammation Increased kynurenine/tryptophan ratio	Ezpeleta et al. (2017)
Systemic LPS challenge (mice)	Increased mortality Impaired leukocyte recruitment Altered inflammatory signaling	Liu et al. (2014)
Systemic LPS challenge (goats)	Prolonged sickness behavior Altered type I interferon response Increased pro-inflammatory signaling	(Salvesen et al. 2017a, 2017b)
Experimentally induced colitis	Weight loss and colonic shortening[a] Increased colonic epithelial damage[a] Increased pro-inflammatory signaling[a]	Martin et al. (2011)

[a] Compared with PrP^C overexpressing mice.

modulation of brain cytokine signaling before and independent of cell damage. A cytoprotective function of PrP^C against damaging inflammatory signaling is also observed in tissues with medium-to-low endogenous expression of PrP^C. This probably reflects altered pro-inflammatory signaling of PrP^C-positive invading immune cells. In immune-privileged tissues, like brain and testicle, the high endogenous expression of PrP^C will further increase tissue protection against deleterious inflammatory damage. Although the participation of PrP^C in immunomodulatory signaling both at resting state and under inflammatory challenge has been convincingly demonstrated, most studies are observational. Hard "molecular facts", in terms of concrete signaling pathways and PrP^C-interacting molecules and downstream effects of these interactions, have generally not yet been elucidated. Investigations of PrP^C functions in neuroimmune crosstalk are in their infancy, meaning this exciting field of research remains open to new ideas and novel approaches.

As illustrated in this review, PrP^C physiology is a puzzle, with bits and pieces of information derived from a multitude of experimental approaches and animal models. The emerging picture might seem more confusing and inconsistent than it actually is. Some of the contradictions and apparent inconsistencies probably reflect limitations and imperfection of the model systems used, rather than true PrP^C physiological phenotypes. This has been demonstrated with the latest lines of PrP^c-deficient transgenic mice and illustrates the importance of constantly updating and refining the toolbox. Independent cross-validation of datasets derived from state-of-the-art experimental modalities, spanning from animal experiments to molecular and biochemical analyses along with the world of "omics", is one way of moving forward in the tedious struggle of putting the pieces together.

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Declarations of interests

None.

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References

Adle-Biassette, H., Verney, C., Peoc'h, K., Dauge, M.C., Razavi, F., Choudat, L., Gressens, P., Budka, H., Henin, D., 2006. Immunohistochemical expression of prion protein (PrP^C) in the human forebrain during development. J. Neuropathol. Exp. Neurol. 65, 698–706.
Altmeppen, H.C., Prox, J., Puig, B., Kluth, M.A., Bernreuther, C., Thurm, D., Jorissen, E., et al., 2011. Lack of a-disintegrin-and-metalloproteinase ADAM10 leads to intracellular accumulation and loss of shedding of the cellular prion protein *in vivo*. Mol. Neurodegener. 6, 36.
Altmeppen, H.C., Prox, J., Puig, B., Dohler, F., Falker, C., Krasemann, S., Glatzel, M., 2013. Roles of endoproteolytic alpha-cleavage and shedding of the prion protein in neurodegeneration. FEBS J. 280, 4338–4347.
Anantharam, V., Kanthasamy, A., Choi, C.J., Martin, D.P., Latchoumycandane, C., Richt, J.A., Kanthasamy, A.G., 2008. Opposing roles of prion protein in oxidative stress- and ER stress-induced apoptotic signaling. Free Radic. Biol. Med. 45, 1530–1541.
Arantes, C., Nomizo, R., Lopes, M.H., Hajj, G.N., Lima, F.R., Martins, V.R., 2009. Prion protein and its ligand stress inducible protein 1 regulate astrocyte development. Glia 57, 1439–1449.
Bainbridge, J., Walker, K.B., 2005. The normal cellular form of prion protein modulates T cell responses. Immunol. Lett. 96, 147–150.
Bakkebø, M.K., Mouillet-Richard, S., Espenes, A., Goldmann, W., Tatzelt, J., Tranulis, M.A., 2015. The cellular prion protein: a player in immunological quiescence. Front. Immunol. 6, 450.
Ballerini, C., Gourdain, P., Bachy, V., Blanchard, N., Levavasseur, E., Gregoire, S., Fontes, P., Aucouturier, P., Hivroz, C., Carnaud, C., 2006. Functional implication of cellular prion protein in antigen-driven interactions between T cells and dendritic cells. J. Immunol. 176, 7254–7262.
Barclay, G.R., Houston, E.F., Halliday, S.I., Farquhar, C.F., Turner, M.L., 2002. Comparative analysis of normal prion protein expression on human, rodent, and ruminant blood cells by using a panel of prion antibodies. Transfusion (Paris) 42, 517–526.
Béland, M., Roucou, X., 2012. The prion protein unstructured N-terminal region is a broad-spectrum molecular sensor with diverse and contrasting potential functions. J. Neurochem. 120, 853–868.
Benestad, S.L., Austbø, L., Tranulis, M.A., Espenes, A., Olsaker, I., 2012. Healthy goats naturally devoid of prion protein. Vet. Res. 43, 87.
Beraldo, F.H., Arantes, C.P., Santos, T.G., Queiroz, N.G., Young, K., Rylett, R.J., Markus, R.P., Prado, M.A., Martins, V.R., 2010. Role of alpha7 nicotinic acetylcholine receptor in calcium signaling induced by prion protein interaction with stress-inducible protein 1. J. Biol. Chem. 285, 36542–36550.
Beraldo, F.H., Arantes, C.P., Santos, T.G., Machado, C.F., Roffe, M., Hajj, G.N., Lee, K.S., et al., 2011. Metabotropic glutamate receptors transduce signals for neurite outgrowth after binding of the prion protein to laminin γ1 chain. Faseb. J. 25, 265–279.
Beraldo, F.H., Soares, I.N., Goncalves, D.F., Fan, J., Thomas, A.A., Santos, T.G., Mohammad, A.H., et al., 2013. Stress-inducible phosphoprotein 1 has unique cochaperone activity during development and regulates cellular response to ischemia via the prion protein. Faseb. J. 27, 3594–3607.
Beraldo, F.H., Ostapchenko, V.G., Xu, J.Z., Di Guglielmo, G.M., Fan, J., Nicholls, P.J., Caron, M.G., Prado, V.F., Prado, M.A.M., 2018. Mechanisms of neuroprotection against ischemic insult by stress-inducible phosphoprotein-1/prion protein complex. J. Neurochem. 145, 68–79.
Bertuchi, F.R., Bourgeon, D.M., Landemberger, M.C., Martins, V.R., Cerchiaro, G., 2012. PrP^C displays an essential protective role from oxidative stress in an astrocyte cell line derived from PrP^C knockout mice. Biochem. Biophys. Res. Commun. 418, 27–32.
Beura, L.K., Hamilton, S.E., Bi, K., Schenkel, J.M., Odumade, O.A., Casey, K.A.,

Thompson, E.A., et al., 2016. Normalizing the environment recapitulates adult human immune traits in laboratory mice. Nature 532, 512–516.
Bi, F., Huang, C., Tong, J., Qiu, G., Huang, B., Wu, Q., Li, F., et al., 2013. Reactive astrocytes secrete lcn2 to promote neuron death. Proc. Natl. Acad. Sci. U. S. A. 110, 4069–4074.
Brandner, S., Isenmann, S., Raeber, A., Fischer, M., Sailer, A., Kobayashi, Y., Marino, S., Weissmann, C., Aguzzi, A., 1996. Normal host prion protein necessary for scrapie-induced neurotoxicity. Nature 379, 339–343.
Bravard, A., Auvré, F., Fantini, D., Bernardino-Sgherri, J., Sissoëff, L., Daynac, M., Xu, Z., et al., 2015. The prion protein is critical for DNA repair and cell survival after genotoxic stress. Nucleic Acids Res. 43, 904–916.
Bremer, J., Baumann, F., Tiberi, C., Wessig, C., Fischer, H., Schwarz, P., Steele, A.D., et al., 2010. Axonal prion protein is required for peripheral myelin maintenance. Nat. Neurosci. 13, 310–318.
Bribián, A., Fontana, X., Llorens, F., Gavin, R., Reina, M., García-Verdugo, J.M., Torres, J.M., de Castro, F., del Río, J.A., 2012. Role of the cellular prion protein in oligodendrocyte precursor cell proliferation and differentiation in the developing and adult mouse CNS. PLoS One 7, e33872.
Brown, D.R., Besinger, A., Herms, J.W., Kretzschmar, H.A., 1998. Microglial expression of the prion protein. Neuroreport 9, 1425–1429.
Büdefeld, T., Majer, A., Jerin, A., Majdic, G., 2014. Deletion of the prion gene *Prnp* affects offensive aggression in mice. Behav. Brain Res. 266, 216–221.
Büeler, H., Fischer, M., Lang, Y., Bluethmann, H., Lipp, H.P., DeArmond, S.J., Prusiner, S.B., Aguet, M., Weissmann, C., 1992. Normal development and behaviour of mice lacking the neuronal cell-surface PrP protein. Nature 356, 577–582.
Büeler, H., Aguzzi, A., Sailer, A., Greiner, R.A., Autenried, P., Aguet, M., Weissmann, C., 1993. Mice devoid of PrP are resistant to scrapie. Cell 73, 1339–1347.
Calzolai, L., Lysek, D.A., Pérez, D.R., Güntert, P., Wüthrich, K., 2005. Prion protein NMR structures of chickens, turtles, and frogs. Proc. Natl. Acad. Sci. U. S. A. 102, 651–655.
Carulla, P., Bribián, A., Rangel, A., Gavín, R., Ferrer, I., Caelles, C., Del Río, J.A., Llorens, F., 2011. Neuroprotective role of PrP^{C} against kainate-induced epileptic seizures and cell death depends on the modulation of JNK3 activation by GluR6/7-PSD-95 binding. Mol. Biol. Cell 22, 3041–3054.
Cashman, N.R., Loertscher, R., Nalbantoglu, J., Shaw, I., Kascsak, R.J., Bolton, D.C., Bendheim, P.E., 1990. Cellular isoform of the scrapie agent protein participates in lymphocyte activation. Cell 61, 185–192.
Castle, A.R., Gill, A.C., 2017. Physiological functions of the cellular prion protein. Front. Mol. Biosci. 4, 19.
Chen, S.G., Teplow, D.B., Parchi, P., Teller, J.K., Gambetti, P., Autilio-Gambetti, L., 1995. Truncated forms of the human prion protein in normal brain and in prion diseases. J. Biol. Chem. 270, 19173–19180.
Chesebro, B., Trifilo, M., Race, R., Meade-White, K., Teng, C., LaCasse, R., Raymond, L., et al., 2005. Anchorless prion protein results in infectious amyloid disease without clinical scrapie. Science 308, 1435–1439.
Chiarini, L.B., Freitas, A.R., Zanata, S.M., Brentani, R.R., Martins, V.R., Linden, R., 2002. Cellular prion protein transduces neuroprotective signals. EMBO J. 21, 3317–3326.
Coitinho, A.S., Roesler, R., Martins, V.R., Brentani, R.R., Izquierdo, I., 2003. Cellular prion protein ablation impairs behavior as a function of age. Neuroreport 14, 1375–1379.
Colling, S.B., Collinge, J., Jefferys, J.G., 1996. Hippocampal slices from prion protein null mice: disrupted Ca^{2+}-activated K^{+} currents. Neurosci. Lett. 209, 49–52.
Colonna, M., Butovsky, O., 2017. Microglia function in the central nervous system during health and neurodegeneration. Annu. Rev. Immunol. 35, 441–468.
Constantinescu, C.S., Farooqi, N., O'Brien, K., Gran, B., 2011. Experimental autoimmune encephalomyelitis (EAE) as a model for multiple sclerosis (MS). Br. J. Pharmacol. 164, 1079–1106.
Cooper, D., Lindberg, F.P., Gamble, J.R., Brown, E.J., Vadas, M.A., 1995. Transendothelial migration of neutrophils involves integrin-associated protein (CD47). Proc. Natl. Acad. Sci. U. S. A. 92, 3978–3982.
Criado, J.R., Sánchez-Alavez, M., Conti, B., Giacchino, J.L., Wills, D.N., Henriksen, S.J., Race, R., Manson, J.C., Chesebro, B., Oldstone, M.B., 2005. Mice devoid of prion protein have cognitive deficits that are rescued by reconstitution of PrP in neurons. Neurobiol. Dis. 19, 255–265.
Dassanayake, R.P., Schneider, D.A., Herrmann-Hoesing, L.M., Truscott, T.C., Davis, W.C., O'Rourke, K.I., 2012. Cell-surface expression of PrP^{C} and the presence of scrapie prions in the blood of goats. J. Gen. Virol. 93, 1127–1131.
de Almeida, C.J., Chiarini, L.B., da Silva, J.P., Silva, P.M.E., Martins, M.A., Linden, R., 2005. The cellular prion protein modulates phagocytosis and inflammatory response. J. Leukoc. Biol. 77, 238–246.
de Vries, H.E., Hendriks, J.J., Honing, H., De Lavalette, C.R., van der Pol, S.M., Hooijberg, E., Dijkstra, C.D., van den Berg, T.K., 2002. Signal-regulatory protein α-CD47 interactions are required for the transmigration of monocytes across cerebral endothelium. J. Immunol. 168, 5832–5839.
Ding, T., Zhou, X., Kouadir, M., Shi, F., Yang, Y., Liu, J., Wang, M., Yin, X., Yang, L., Zhao, D., 2013. Cellular prion protein participates in the regulation of inflammatory response and apoptosis in BV2 microglia during infection with *Mycobacterium bovis*. J. Mol. Neurosci. 51, 118–126.
Dodelet, V.C., Cashman, N.R., 1998. Prion protein expression in human leukocyte differentiation. Blood 91, 1556–1561.
Doeppner, T.R., Kaltwasser, B., Schlechter, J., Jaschke, J., Kilic, E., Bähr, M., Hermann, D.M., Weise, J., 2015. Cellular prion protein promotes post-ischemic neuronal survival, angioneurogenesis and enhances neural progenitor cell homing via proteasome inhibition. Cell Death Dis. 6, e2024.
Donaldson, D.S., Sehgal, A., Rios, D., Williams, I.R., Mabbott, N.A., 2016. Increased abundance of M cells in the gut epithelium dramatically enhances oral prion disease susceptibility. PLoS Pathog. 12, e1006075.
Dong, H., Zhang, X., Qian, Y., 2014. Mast cells and neuroinflammation. Med. Sci. Monit. Basic Res. 20, 200–206.
Donne, D.G., Viles, J.H., Groth, D., Mehlhorn, I., James, T.L., Cohen, F.E., Prusiner, S.B., Wright, P.E., Dyson, H.J., 1997. Structure of the recombinant full-length hamster prion protein PrP(29-231): the N terminus is highly flexible. Proc. Natl. Acad. Sci. U. S. A. 94, 13452–13457.
Dupiereux, I., Falisse-Poirrier, N., Zorzi, W., Watt, N.T., Thellin, O., Zorzi, D., Pierard, O., Hooper, N.M., Heinen, E., Elmoualij, B., 2008. Protective effect of prion protein via the N-terminal region in mediating a protective effect on paraquat-induced oxidative injury in neuronal cells. J. Neurosci. Res. 86, 653–659.
Dürig, J., Giese, A., Schulz-Schaeffer, W., Rosenthal, C., Schmücker, U., Bieschke, J., Dührsen, U., Kretzschmar, H.A., 2000. Differential constitutive and activation-dependent expression of prion protein in human peripheral blood leucocytes. Br. J. Haematol. 108, 488–495.
Ezpeleta, J., Boudet-Devaud, F., Pietri, M., Baudry, A., Baudouin, V., Alleaume-Butaux, A., Dagoneau, N., Kellermann, O., Launay, J.M., Schneider, B., 2017. Protective role of cellular prion protein against TNFα-mediated inflammation through TACE alpha-secretase. Sci. Rep. 7, 7671.
Ferreira, D.G., Temido-Ferreira, M., Vicente Miranda, H., Batalha, V.L., Coelho, J.E., Szegö, E.M., Marques-Morgado, I., et al., 2017. α-synuclein interacts with PrP^{C} to induce cognitive impairment through mGluR5 and NMDAR2B. Nat. Neurosci. 20, 1569–1579.
Gabus, C., Derrington, E., Leblanc, P., Chnaiderman, J., Dormont, D., Swietnicki, W., Morillas, M., et al., 2001. The prion protein has RNA binding and chaperoning properties characteristic of nucleocapsid protein NCP7 of HIV-1. J. Biol. Chem. 276, 19301–19309.
Gadotti, V.M., Bonfield, S.P., Zamponi, G.W., 2012. Depressive-like behaviour of mice lacking cellular prion protein. Behav. Brain Res. 227, 319–323.
Gasperini, L., Meneghetti, E., Pastore, B., Benetti, F., Legname, G., 2015. Prion protein and copper cooperatively protect neurons by modulating NMDA receptor through S-nitrosylation. Antioxid Redox Signal 22, 772–784.
Gourdain, P., Ballerini, C., Nicot, A.B., Carnaud, C., 2012. Exacerbation of experimental autoimmune encephalomyelitis in prion protein (PrP^{C})-null mice: evidence for a critical role of the central nervous system. J. Neuroinflammation 9, 25.
Guillot-Sestier, M.V., Sunyach, C., Druon, C., Scarzello, S., Checler, F., 2009. The alpha-secretase-derived N-terminal product of cellular prion, N1, displays neuroprotective function *in vitro* and *in vivo*. J. Biol. Chem. 284, 35973–35986.
Haddon, D.J., Hughes, M.R., Antignano, F., Westaway, D., Cashman, N.R., McNagny, K.M., 2009. Prion protein expression and release by mast cells after activation. J. Infect. Dis. 200, 827–831.
Haigh, C.L., Drew, S.C., Boland, M.P., Masters, C.L., Barnham, K.J., Lawson, V.A., Collins, S.J., 2009. Dominant roles of the polybasic proline motif and copper in the PrP23-89-mediated stress protection response. J. Cell Sci. 122, 1518–1528.
Hajj, G.N., Arantes, C.P., Dias, M.V., Roffé, M., Costa-Silva, B., Lopes, M.H., Porto-Carreiro, I., et al., 2013. The unconventional secretion of stress-inducible protein 1 by a heterogeneous population of extracellular vesicles. Cell. Mol. Life Sci. 70, 3211–3227.
Halliday, S., Houston, F., Hunter, N., 2005. Expression of PrP^{C} on cellular components of sheep blood. J. Gen. Virol. 86, 1571–1579.
Harris, D.A., Huber, M.T., van Dijken, P., Shyng, S.L., Chait, B.T., Wang, R., 1993. Processing of a cellular prion protein: identification of N- and C-terminal cleavage sites. Biochemistry 32, 1009–1016.
Hartmann, C.A., Martins, V.R., Lima, F.R., 2013. High levels of cellular prion protein improve astrocyte development. FEBS Lett. 587, 238–244.
Heikenwalder, M., Zeller, N., Seeger, H., Prinz, M., Klöhn, P.C., Schwarz, P., Ruddle, N.H., Weissmann, C., Aguzzi, A., 2005. Chronic lymphocytic inflammation specifies the organ tropism of prions. Science 307, 1107–1110.
Herrmann, L.M., Davis, W.C., Knowles, D.P., Wardrop, K.J., Sy, M.S., Gambetti, P., O'Rourke, K.I., 2001. Cellular prion protein is expressed on peripheral blood mononuclear cells but not platelets of normal and scrapie-infected sheep. Haematologica 86, 146–153.
Holada, K., Vostal, J.G., 2000. Different levels of prion protein (PrP^{C}) expression on hamster, mouse and human blood cells. Br. J. Haematol. 110, 472–480.
Hornshaw, M.P., McDermott, J.R., Candy, J.M., 1995. Copper binding to the N-terminal tandem repeat regions of mammalian and avian prion protein. Biochem. Biophys. Res. Commun. 207, 621–629.
Horvath, R.J., Nutile-McMenemy, N., Alkaitis, M.S., Deleo, J.A., 2008. Differential migration, LPS-induced cytokine, chemokine, and NO expression in immortalized BV-2 and HAPI cell lines and primary microglial cultures. J. Neurochem. 107, 557–569.
Hoshino, S., Inoue, K., Yokoyama, T., Kobayashi, S., Asakura, T., Teramoto, A., 2003. Prions prevent brain damage after experimental brain injury: a preliminary report. Acta Neurochir. Suppl. 86, 297–299.
Hu, W., Nessler, S., Hemmer, B., Eagar, T.N., Kane, L.P., Leliveld, S.R., Müller-Schiffmann, A., et al., 2010. Pharmacological prion protein silencing accelerates central nervous system autoimmune disease via T cell receptor signalling. Brain 133, 375–388.
Huber, R., Deboer, T., Tobler, I., 1999. Prion protein: a role in sleep regulation? J. Sleep Res. 8, 30–36.
Ivashkiv, L.B., Donlin, L.T., 2014. Regulation of type I interferon responses. Nat. Rev. Immunol. 14, 36–49.
Jeon, J.W., Park, B.C., Jung, J.G., Jang, Y.S., Shin, E.C., Park, Y.W., 2013. The soluble form of the cellular prion protein enhances phagocytic activity and cytokine production by human monocytes via activation of ERK and NF-κB. Immune Netw. 13, 148–156.
Jin, R., Yang, G., Li, G., 2010. Inflammatory mechanisms in ischemic stroke: role of inflammatory cells. J. Leukoc. Biol. 87, 779–789.

Khosravani, H., Zhang, Y., Tsutsui, S., Hameed, S., Altier, C., Hamid, J., Chen, L., et al., 2008. Prion protein attenuates excitotoxicity by inhibiting NMDA receptors. J. Cell Biol. 181, 551–565.
Kim, J.H., Min, K.J., Seol, W., Jou, I., Joe, E.H., 2010. Astrocytes in injury states rapidly produce anti-inflammatory factors and attenuate microglial inflammatory responses. J. Neurochem. 115, 1161–1171.
Kovacs, G.G., Budka, H., 2008. Prion diseases: from protein to cell pathology. Am. J. Pathol. 172, 555–565.
Krebs, B., Dorner-Ciossek, C., Schmalzbauer, R., Vassallo, N., Herms, J., Kretzschmar, H.A., 2006. Prion protein induced signaling cascades in monocytes. Biochem. Biophys. Res. Commun. 340, 13–22.
Küffer, A., Lakkaraju, A.K., Mogha, A., Petersen, S.C., Airich, K., Doucerain, C., Marpakwar, R., et al., 2016. The prion protein is an agonistic ligand of the G protein-coupled receptor Adgrg6. Nature 536, 464–468.
Lathe, R., Darlix, J., 2017. Prion protein PRNP: a new player in innate immunity? The Aβ connection. J. Alzheimers Dis. 1, 263–275.
Latour, S., Tanaka, H., Demeure, C., Mateo, V., Rubio, M., Brown, E.J., Maliszewski, C., et al., 2001. Bidirectional negative regulation of human T and dendritic cells by CD47 and its cognate receptor signal-regulator protein-alpha: down-regulation of IL-12 responsiveness and inhibition of dendritic cell activation. J. Immunol. 167, 2547–2554.
Lauren, J., Gimbel, D.A., Nygaard, H.B., Gilbert, J.W., Strittmatter, S.M., 2009. Cellular prion protein mediates impairment of synaptic plasticity by amyloid-beta oligomers. Nature 457, 1128–1132.
Lee, S.D., Lai, T.W., Lin, S.Z., Lin, C.H., Hsu, Y.H., Li, C.Y., Wang, H.J., et al., 2013. Role of stress-inducible protein-1 in recruitment of bone marrow derived cells into the ischemic brains. EMBO Mol. Med. 5, 1227–1246.
CC License. https://creativecommons.org/licenses/by/2.0/(Accessed 20. June 2018).
Lima, F.R., Arantes, C.P., Muras, A.G., Nomizo, R., Brentani, R.R., Martins, V.R., 2007. Cellular prion protein expression in astrocytes modulates neuronal survival and differentiation. J. Neurochem. 103, 2164–2176.
Linden, R., 2017. The biological function of the prion protein: a cell surface scaffold of signaling modules. Front. Mol. Neurosci. 10, 77.
Linden, R., Martins, V.R., Prado, M.A., Cammarota, M., Izquierdo, I., Brentani, R.R., 2008. Physiology of the prion protein. Physiol. Rev. 88, 673–728.
Linsenmeier, L., Altmeppen, H.C., Wetzel, S., Mohammadi, B., Saftig, P., Glatzel, M., 2017. Diverse functions of the prion protein - does proteolytic processing hold the key? Biochim. Biophys. Acta 1864, 2128–2137.
Liu, J., Zhao, D., Liu, C., Ding, T., Yang, L., Yin, X., Zhou, X., 2014. Prion protein participates in the protection of mice from lipopolysaccharide infection by regulating the inflammatory process. J. Mol. Neurosci. 55, 279–287.
Llorens, F., Carulla, P., Villa, A., Torres, J.M., Fortes, P., Ferrer, I., del Río, J.A., 2013. PrP^{C} regulates epidermal growth factor receptor function and cell shape dynamics in Neuro2a cells. J. Neurochem. 127, 124–138.
Lobão-Soares, B., Walz, R., Carlotti Jr., C.G., Sakamoto, A.C., Calvo, F., Terzian, A.L., da Silva, J.A., Wichert-Ana, L., Coimbra, N.C., Bianchin, M.M., 2007. Cellular prion protein regulates the motor behaviour performance and anxiety-induced responses in genetically modified mice. Behav. Brain Res. 183, 87–94.
Lopes, M.H., Hajj, G.N., Muras, A.G., Mancini, G.L., Castro, R.M., Ribeiro, K.C., Brentani, R.R., Linden, R., Martins, V.R., 2005. Interaction of cellular prion and stress-inducible protein 1 promotes neuritogenesis and neuroprotection by distinct signaling pathways. J. Neurosci. 25, 11330–11339.
Loubet, D., Dakowski, C., Pietri, M., Pradines, E., Bernard, S., Callebert, J., Ardila-Osorio, H., et al., 2012. Neuritogenesis: the prion protein controls beta1 integrin signaling activity. Faseb. J. 26, 678–690.
Lundberg, P., Magzoub, M., Lindberg, M., Hällbrink, M., Jarvet, J., Eriksson, L.E., Langel, U., Gräslund, A., 2002. Cell membrane translocation of the N-terminal (1-28) part of the prion protein. Biochem. Biophys. Res. Commun. 299, 85–90.
Lysek, D.A., Schorn, C., Nivon, L.G., Esteve-Moya, V., Christen, B., Calzolai, L., von Schroetter, C., et al., 2005. Prion protein NMR structures of cats, dogs, pigs, and sheep. Proc. Natl. Acad. Sci. U. S. A. 102, 640–645.
Mabbott, N.A., Brown, K.L., Manson, J., Bruce, M.E., 1997. T-lymphocyte activation and the cellular form of the prion protein. Immunology 92, 161–165.
Malachin, G., Reiten, M.R., Salvesen, Ø., Aanes, H., Kamstra, J.H., Skovgaard, K., Heegaard, P.M.H., et al., 2017. Loss of prion protein induces a primed state of type I interferon-responsive genes. PLoS One 12, e0179881.
Mallucci, G.R., Ratté, S., Asante, E.A., Linehan, J., Gowland, I., Jefferys, J.G., Collinge, J., 2002. Post-natal knockout of prion protein alters hippocampal CA1 properties, but does not result in neurodegeneration. EMBO J. 21, 202–210.
Mallucci, G., Dickinson, A., Linehan, J., Klöhn, P.C., Brandner, S., Collinge, J., 2003. Depleting neuronal PrP in prion infection prevents disease and reverses spongiosis. Science 302, 871–874.
Mange, A., Beranger, F., Peoc'h, K., Onodera, T., Frobert, Y., Lehmann, S., 2004. Alpha- and beta- cleavages of the amino-terminus of the cellular prion protein. Biol. Cell. 96, 125–132.
Manson, J.C., Clarke, A.R., Hooper, M.L., Aitchison, L., McConnell, I., Hope, J., 1994. 129/Ola mice carrying a null mutation in PrP that abolishes mRNA production are developmentally normal. Mol. Neurobiol. 8, 121–127.
Manson, J.C., Hope, J., Clarke, A.R., Johnston, A., Black, C., MacLeod, N., 1995. PrP gene dosage and long term potentiation. Neurodegeneration 4, 113–114.
Manuelidis, L., Sklaviadis, T., Akowitz, A., Fritch, W., 1995. Viral particles are required for infection in neurodegenerative Creutzfeldt-Jakob disease. Proc. Natl. Acad. Sci. U. S. A. 92, 5124–5128.
Mariante, R.M., Nóbrega, A., Martins, R.A., Areal, R.B., Bellio, M., Linden, R., 2012. Neuroimmunoendocrine regulation of the prion protein in neutrophils. J. Biol. Chem. 287, 35506–35515.
Marques, F., Sousa, J.C., Coppola, G., Falcao, A.M., Rodrigues, A.J., Geschwind, D.H., Sousa, N., Correia-Neves, M., Palha, J.A., 2009. Kinetic profile of the transcriptome changes induced in the choroid plexus by peripheral inflammation. J. Cereb. Blood Flow Metab. 29, 921–932.
Martin, G.R., Keenan, C.M., Sharkey, K.A., Jirik, F.R., 2011. Endogenous prion protein attenuates experimentally induced colitis. Am. J. Pathol. 179, 2290–2301.
Mattei, V., Garofalo, T., Misasi, R., Circella, A., Manganelli, V., Lucania, G., Pavan, A., Sorice, M., 2004. Prion protein is a component of the multimolecular signaling complex involved in T cell activation. FEBS Lett. 560, 14–18.
Mays, C.E., Coomaraswamy, J., Watts, J.C., Yang, J., Ko, K.W., Strome, B., Mercer, R.C., Wohlgemuth, S.L., Schmitt-Ulms, G., Westaway, D., 2014a. Endoproteolytic processing of the mammalian prion glycoprotein family. FEBS J. 281, 862–876.
Mays, C.E., Kim, C., Haldiman, T., van der Merwe, J., Lau, A., Yang, J., Grams, J., et al., 2014b. Prion disease tempo determined by host-dependent substrate reduction. J. Clin. Invest. 124, 847–858.
McCulloch, L., Brown, K.L., Bradford, B.M., Hopkins, J., Bailey, M., Rajewsky, K., Manson, J.C., Mabbott, N.A., 2011. Follicular dendritic cell-specific prion protein (PrP) expression alone is sufficient to sustain prion infection in the spleen. PLoS Pathog. 7, e1002402.
McCutcheon, S., Alejo Blanco, A.R., Houston, E.F., de Wolf, C., Tan, B.C., Smith, A., Groschup, M.H., et al., 2011. All clinically-relevant blood components transmit prion disease following a single blood transfusion: a sheep model of vCJD. PLoS One 6, e23169.
McMahon, H.E., Mangé, A., Nishida, N., Créminon, C., Casanova, D., Lehmann, S., 2001. Cleavage of the amino terminus of the prion protein by reactive oxygen species. J. Biol. Chem. 276, 2286–2291.
Megra, B.W., Eugenin, E.A., Berman, J.W., 2018. Inflammatory mediators reduce surface PrP^{C} on human BMVEC resulting in decreased barrier integrity. Lab. Invest. 10, 1347–1359.
Meier, P., Genoud, N., Prinz, M., Maissen, M., Rülicke, T., Zurbriggen, A., Raeber, A.J., Aguzzi, A., 2003. Soluble dimeric prion protein binds PrP^{Sc} *in vivo* and antagonizes prion disease. Cell 113, 49–60.
Mitteregger, G., Vosko, M., Krebs, B., Xiang, W., Kohlmannsperger, V., Nölting, S., Hamann, G.F., Kretzschmar, H.A., 2007. The role of the octarepeat region in neuroprotective function of the cellular prion protein. Brain Pathol. 17, 174–183.
Moser, M., Colello, R.J., Pott, U., Oesch, B., 1995. Developmental expression of the prion protein gene in glial cells. Neuron 14, 509–517.
Murdoch, G.H., Sklaviadis, T., Manuelidis, E.E., Manuelidis, L., 1990. Potential retroviral RNAs in Creutzfeldt-Jakob disease. J. Virol. 64, 1477–1486.
Nasu-Nishimura, Y., Taniuchi, Y., Nishimura, T., Sakudo, A., Nakajima, K., Ano, Y., Sugiura, K., Sakaguchi, S., Itohara, S., Onodera, T., 2008. Cellular prion protein prevents brain damage after encephalomyocarditis virus infection in mice. Arch. Virol. 153, 1007–1012.
Nico, P.B., de-Paris, F., Vinadé, E.R., Amaral, O.B., Rockenbach, I., Soares, B.L., Guarnieri, R., et al., 2005. Altered behavioural response to acute stress in mice lacking cellular prion protein. Behav. Brain Res. 162, 173–181.
Nuvolone, M., Kana, V., Hutter, G., Sakata, D., Mortin-Toth, S.M., Russo, G., Danska, J.S., Aguzzi, A., 2013. SIRPα polymorphisms, but not the prion protein, control phagocytosis of apoptotic cells. J. Exp. Med. 210, 2539–2552.
Nuvolone, M., Hermann, M., Sorce, S., Russo, G., Tiberi, C., Schwarz, P., Minikel, E., Sanoudou, D., Pelczar, P., Aguzzi, A., 2016. Strictly co-isogenic C57BL/6J-*Prnp*$^{-/-}$ mice: a rigorous resource for prion science. J. Exp. Med. 213, 313–327.
Parizek, P., Roeckl, C., Weber, J., Flechsig, E., Aguzzi, A., Raeber, A.J., 2001. Similar turnover and shedding of the cellular prion protein in primary lymphoid and neuronal cells. J. Biol. Chem. 276, 44627–44632.
Pinheiro, L.P., Linden, R., Mariante, R.M., 2015. Activation and function of murine primary microglia in the absence of the prion protein. J. Neuroimmunol. 286, 25–32.
Prusiner, S.B., 1982. Novel proteinaceous infectious particles cause scrapie. Science 216, 136–144.
Prusiner, S.B., Groth, D., Serban, A., Koehler, R., Foster, D., Torchia, M., Burton, D., Yang, S.L., DeArmond, S.J., 1993. Ablation of the prion protein (PrP) gene in mice prevents scrapie and facilitates production of anti-PrP antibodies. Proc. Natl. Acad. Sci. U. S. A. 90, 10608–10612.
Purro, S.A., Nicoll, A.J., Collinge, J., 2018. Prion protein as a toxic acceptor of amyloid-beta oligomers. Biol. Psychiatry 83, 358–368.
Rambold, A.S., Müller, V., Ron, U., Ben-Tal, N., Winklhofer, K.F., Tatzelt, J., 2008. Stress-protective signalling of prion protein is corrupted by scrapie prions. EMBO J. 27, 1974–1984.
Reiten, M.R., Bakkebø, M.K., Brun-Hansen, H., Lewandowska-Sabat, A.M., Olsaker, I., Tranulis, M.A., Espenes, A., Boysen, P., 2015. Hematological shift in goat kids naturally devoid of prion protein. Front. Cell Dev. Biol. 3, 44.
Resenberger, U.K., Harmeier, A., Woerner, A.C., Goodman, J.L., Muller, V., Krishnan, R., Vabulas, R.M., et al., 2011. The cellular prion protein mediates neurotoxic signalling of beta-sheet-rich conformers independent of prion replication. EMBO J. 30, 2057–2070.
Rial, D., Duarte, F.S., Xikota, J.C., Schmitz, A.E., Dafré, A.L., Figueiredo, C.P., Walz, R., Prediger, R.D., 2009. Cellular prion protein modulates age-related behavioral and neurochemical alterations in mice. Neuroscience 164, 896–907.
Richardson, D.D., Tol, S., Valle-Encinas, E., Pleguezuelos, C., Bierings, R., Geerts, D., Fernandez-Borja, M., 2015. The prion protein inhibits monocytic cell migration by stimulating β1 integrin adhesion and uropod formation. J. Cell Sci. 128, 3018–3029.
Richt, J.A., Kasinathan, P., Hamir, A.N., Castilla, J., Sathiyaseelan, T., Vargas, F., Sathiyaseelan, J., et al., 2007. Production of cattle lacking prion protein. Nat. Biotechnol. 25, 132–138.
Riek, R., Hornemann, S., Wider, G., Billeter, M., Glockshuber, R., Wüthrich, K., 1996. NMR structure of the mouse prion protein domain PrP(121-231). Nature 382,

180–182.
Riek, R., Hornemann, S., Wider, G., Glockshuber, R., Wüthrich, K., 1997. NMR characterization of the full-length recombinant murine prion protein, mPrP(23-231). FEBS Lett. 413, 282–288.
Roesler, R., Walz, R., Quevedo, J., de-Paris, F., Zanata, S.M., Graner, E., Izquierdo, I., Martins, V.R., Brentani, R.R., 1999. Normal inhibitory avoidance learning and anxiety, but increased locomotor activity in mice devoid of PrP^{C}. Brain Res. Mol. Brain Res. 71, 349–353.
Rungta, R.L., Charpak, S., 2016. Astrocyte endfeet march to the beat of different vessels. Nat. Neurosci. 19, 1539–1541.
Salvesen, Ø., Reiten, M.R., Espenes, A., Bakkebø, M.K., Tranulis, M.A., Ersdal, C., 2017a. LPS-induced systemic inflammation reveals an immunomodulatory role for the prion protein at the blood-brain interface. J. Neuroinflammation 14, 106.
Salvesen, Ø., Reiten, M.R., Kamstra, J.H., Bakkebø, M.K., Espenes, A., Tranulis, M.A., Ersdal, C., 2017b. Goats without prion protein display enhanced proinflammatory pulmonary signaling and extracellular matrix remodeling upon systemic lipopolysaccharide challenge. Front. Immunol. 8.
Sánchez-Alavez, M., Conti, B., Moroncini, G., Criado, J.R., 2007. Contributions of neuronal prion protein on sleep recovery and stress response following sleep deprivation. Brain Res. 1158, 71–80.
Santuccione, A., Sytnyk, V., Leshchyns'ka, I., Schachner, M., 2005. Prion protein recruits its neuronal receptor NCAM to lipid rafts to activate p59fyn and to enhance neurite outgrowth. J. Cell Biol. 169, 341–354.
Schmitz, M., Greis, C., Ottis, P., Silva, C.J., Schulz-Schaeffer, W.J., Wrede, A., Koppe, K., et al., 2014. Loss of prion protein leads to age-dependent behavioral abnormalities and changes in cytoskeletal protein expression. Mol. Neurobiol. 50, 923–936.
Senator, A., Rachidi, W., Lehmann, S., Favier, A., Benboubetra, M., 2004. Prion protein protects against DNA damage induced by paraquat in cultured cells. Free Radic. Biol. Med. 37, 1224–1230.
Seong, Y.J., Sung, P.S., Jang, Y.S., Choi, Y.J., Park, B.C., Park, S.H., Park, Y.W., Shin, E.C., 2015. Activation of human natural killer cells by the soluble form of cellular prion protein. Biochem. Biophys. Res. Commun. 464, 512–518.
Shi, F., Yang, L., Kouadir, M., Yang, Y., Ding, T., Wang, J., Zhou, X., Yin, X., Zhao, D., 2013. Prion protein participates in the regulation of classical and alternative activation of BV2 microglia. J. Neurochem. 124, 168–174.
Shyu, W.C., Lin, S.Z., Chiang, M.F., Ding, D.C., Li, K.W., Chen, S.F., Yang, H.I., Li, H., 2005. Overexpression of PrP^{C} by adenovirus-mediated gene targeting reduces ischemic injury in a stroke rat model. J. Neurosci. 25, 8967–8977.
Singh, A., Kong, Q., Luo, X., Petersen, R.B., Meyerson, H., Singh, N., 2009. Prion protein (PrP) knock-out mice show altered iron metabolism: a functional role for PrP in iron uptake and transport. PLoS One 4, e6115.
Sklaviadis, T., Akowitz, A., Manuelidis, E.E., Manuelidis, L., 1993. Nucleic acid binding proteins in highly purified Creutzfeldt-Jakob disease preparations. Proc. Natl. Acad. Sci. U. S. A. 90, 5713–5717.
Smith, R.E., Patel, V., Seatter, S.D., Deehan, M.R., Brown, M.H., Brooke, G.P., Goodridge, H.S., et al., 2003. A novel MyD-1 (SIRPα) signaling pathway that inhibits LPS-induced TNFα production by monocytes. Blood 102, 2532–2540.
Spudich, A., Frigg, R., Kilic, E., Kilic, U., Oesch, B., Raeber, A., Bassetti, C.L., Hermann, D.M., 2005. Aggravation of ischemic brain injury by prion protein deficiency: role of ERK-1/-2 and STAT-1. Neurobiol. Dis. 20, 442–449.
Stahl, N., Baldwin, M.A., Burlingame, A.L., Prusiner, S.B., 1990. Identification of glycoinositol phospholipid linked and truncated forms of the scrapie prion protein. Biochemistry 29, 8879–8884.
Steele, A.D., Zhou, Z., Jackson, W.S., Zhu, C., Auluck, P., Moskowitz, M.A., Chesselet, M.F., Lindquist, S., 2009. Context dependent neuroprotective properties of prion protein (PrP). Prion 3, 240–249.
Stöhr, J., Watts, J.C., Legname, G., Oehler, A., Lemus, A., Nguyen, H.O., Sussman, J., et al., 2011. Spontaneous generation of anchorless prions in transgenic mice. Proc. Natl. Acad. Sci. U. S. A. 108, 21223–21228.
Tatzelt, J., Winklhofer, K.F., 2004. Folding and misfolding of the prion protein in the secretory pathway. Amyloid 11, 162–172.
Tian, L., Ma, L., Kaarela, T., Li, Z., 2012. Neuroimmune crosstalk in the central nervous system and its significance for neurological diseases. J. Neuroinflammation 9, 155.
Tobler, I., Gaus, S.E., Deboer, T., Achermann, P., Fischer, M., Rülicke, T., Moser, M., Oesch, B., McBride, P.A., Manson, J.C., 1996. Altered circadian activity rhythms and sleep in mice devoid of prion protein. Nature 380, 639–642.
Tsutsui, S., Hahn, J.N., Johnson, T.A., Ali, Z., Jirik, F.R., 2008. Absence of the cellular prion protein exacerbates and prolongs neuroinflammation in experimental autoimmune encephalomyelitis. Am. J. Pathol. 173, 1029–1041.
Uraki, R., Sakudo, A., Ando, S., Kitani, H., Onodera, T., 2010. Enhancement of phagocytotic activity by prion protein in PrP-deficient macrophage cells. Int. J. Mol. Med. 26, 527–532.
van Beek, E.M., Cochrane, F., Barclay, A.N., van den Berg, T.K., 2005. Signal regulatory proteins in the immune system. J. Immunol. 175, 7781–7787.
Wadia, J.S., Schaller, M., Williamson, R.A., Dowdy, S.F., 2008. Pathologic prion protein infects cells by lipid-raft dependent macropinocytosis. PLoS One 3, e3314.
Wang, M., Zhao, D., Yang, Y., Liu, J., Wang, J., Yin, X., Yang, L., Zhou, X., 2014. The cellular prion protein negatively regulates phagocytosis and cytokine expression in murine bone marrow-derived macrophages. PLoS One 9, e102785.
Watt, N.T., Routledge, M.N., Wild, C.P., Hooper, N.M., 2007. Cellular prion protein protects against reactive-oxygen-species-induced DNA damage. Free Radic. Biol. Med. 43, 959–967.
Watt, N.T., Taylor, D.R., Kerrigan, T.L., Griffiths, H.H., Rushworth, J.V., Whitehouse, I.J., Hooper, N.M., 2012. Prion protein facilitates uptake of zinc into neuronal cells. Nat. Commun. 3, 1134.
Weise, J., Crome, O., Sandau, R., Schulz-Schaeffer, W., Bähr, M., Zerr, I., 2004. Upregulation of cellular prion protein (PrP^{C}) after focal cerebral ischemia and influence of lesion severity. Neurosci. Lett. 372, 146–150.
Weise, J., Sandau, R., Schwarting, S., Crome, O., Wrede, A., Schulz-Schaeffer, W., Zerr, I., Bähr, M., 2006. Deletion of cellular prion protein results in reduced Akt activation, enhanced postischemic caspase-3 activation, and exacerbation of ischemic brain injury. Stroke 37, 1296–1300.
Weise, J., Doeppner, T.R., Müller, T., Wrede, A., Schulz-Schaeffer, W., Zerr, I., Witte, O.W., Bähr, M., 2008. Overexpression of cellular prion protein alters postischemic Erk1/2 phosphorylation but not Akt phosphorylation and protects against focal cerebral ischemia. Restor. Neurol. Neurosci. 26, 57–64.
Winklhofer, K.F., Tatzelt, J., Haass, C., 2008. The two faces of protein misfolding: gain- and loss-of-function in neurodegenerative diseases. EMBO J. 27, 336–349.
Wu, G.R., Mu, T.C., Gao, Z.X., Wang, J., Sy, M.S., Li, C.Y., 2017. Prion protein is required for tumor necrosis factor α (TNFα)-triggered nuclear factor κB (NF-κB) signaling and cytokine production. J. Biol. Chem. 292, 18747–18759.
Wulf, M.A., Senatore, A., Aguzzi, A., 2017. The biological function of the cellular prion protein: an update. BMC Biol. 15, 34.
Yang, X., Yang, S., Zhang, J., Xue, L., Hu, Z., 2002. Role of caspase 3 in neuronal apoptosis after acute brain injury. Chin. J. Traumatol. 5, 250–253.
Zahn, R., Liu, A., Lührs, T., Riek, R., von Schroetter, C., López García, F., Billeter, M., Calzolai, L., Wider, G., Wüthrich, K., 2000. NMR solution structure of the human prion protein. Proc. Natl. Acad. Sci. U. S. A. 97, 145–150.
Zanata, S.M., Lopes, M.H., Mercadante, A.F., Hajj, G.N., Chiarini, L.B., Nomizo, R., Freitas, A.R., et al., 2002. Stress-inducible protein 1 is a cell surface ligand for cellular prion that triggers neuroprotection. EMBO J. 21, 3307–3316.
Zhang, C.C., Steele, A.D., Lindquist, S., Lodish, H.F., 2006. Prion protein is expressed on long-term repopulating hematopoietic stem cells and is important for their self-renewal. Proc. Natl. Acad. Sci. U. S. A. 103, 2184–2189.