The cellular prion protein beyond prion diseases

Manni Giorgia, Lewis Victoria, Senesi Matteo, Spagnolli Giovanni, Fallarino Francesca, Collins Steven J, Mouillet-Richard Sophie, Biasini Emiliano

Introduction

Aging is accompanied by molecular, cellular and functional changes, which particularly affect the nervous system. Among the physiological processes known to be altered by aging is the protein folding quality control machinery, deputed to monitor and ameliorate protein misfolding. Once present, misfolded proteins typically acquire alternative conformations that can lead to their aggregation and accumulation intracellularly or extracellularly, and eventually initiate a cascade of toxic molecular events, ultimately resulting in cellular dysfunction [1]. A wide range of age-related disorders is indeed linked to protein misfolding and aggregation in the brain. Examples include highly prevalent disorders such as Parkinson’s and Alzheimer’s diseases, as well as rarer disorders such as prion diseases. Alzheimer’s disease is the most common form of dementia in the elderly population, currently affecting almost 40 million individuals worldwide. The number will increase dramatically in the coming decades as the population ages, producing challenging medical and socioeconomic consequences [2].

According to the amyloid cascade hypothesis, Alzheimer’s disease is a consequence of the accumulation in the brain of the 40–42 amino acid Aβ peptide, a cleavage product of the amyloid precursor protein (APP). The Aβ peptide spontaneously forms polymers ranging from small, soluble oligomers to large, insoluble fibrils [3]. Multiple pieces of evidence suggest that soluble Aβ oligomers, rather than fibrillar aggregates, are primarily responsible for the synaptic dysfunction underlying the cognitive decline in Alzheimer’s disease [4]. Aβ oligomers are believed to act, at least in part, by binding to cell surface receptors that transduce their detrimental effects on synapses. Recently, a novel candidate has emerged as a receptor for Aβ oligomers: the cellular form of the prion protein (PrPSc) [5]. PrPSc, an endogenous, cell-surface glycoprotein, plays a central role in transmissible neurodegenerative disorders commonly referred to as prion diseases. These diseases, which can be sporadic, inherited or acquired, are caused by the conformational conversion of PrPSc into a misfolded isoform (called scrapie form of PrP or PrPSc) that accumulates in the central nervous system of affected individuals. PrPSc is an infectious protein (“constituting “prions”) that propagates itself by binding to PrPSc triggering its conformational rearrangement (“templating”) into new PrPSc molecules [6]. A great deal of evidence indicates a distinction between prion infectivity and toxicity, and suggests that a physiological function of PrPSc may be altered upon binding to PrPSc, to deliver neurotoxic signals [7]. In fact, the presence of PrPSc on the neuronal surface has been shown to be critical not only for supporting PrPSc propagation, but also for transducing its neurotoxicity [8–10]. This conclusion recently found unexpected support from data involving other pathogenic protein oligomers. Different studies provided evidence that PrPSc could mediate the toxicity of oligomeric assemblies of Aβ, alpha-synuclein and other β-sheet-rich protein conformers [5, 11–14]. These results indicate that misfolded assemblies of several different pathogenic proteins could exert their effects by blocking, enhancing or altering the normal activity of PrPSc [15].

Summary

The cellular prion protein (PrPSc), a cell surface glycoprotein originally identified for its central role in prion diseases (also called transmissible spongiform encephalopathies), has recently been implicated in the pathogenesis of other neurodegenerative disorders, such as Alzheimer’s and Parkinson’s diseases, by acting as a toxicity-transducing receptor for different misfolded protein isoforms, or in some case by exerting neuroprotective effects. Interestingly, PrPSc has also been reported to play unexpected functions outside the nervous system, for example by contributing to myelin homeostasis, regulating specific processes of the immune system and participating in various aspects of cancer progression. Collectively, these observations point to a much broader role for PrPSc in physiological and disease processes than originally assumed. In this manuscript, we provide an overview of what is known about the role of PrPSc beyond prion disorders and discuss the potential implications of targeting this protein in different diseases.

Keywords: cellular prion protein, prion disease, neurodegeneration, immune system, cancer
Conclusion highlights a close connection between the role of PrP(C) in several neurodegenerative diseases and its physiological function. What is this function? Several activities have been attributed to PrP(C) in the nervous system, mostly based on subtle abnormalities detected in mice or cells depleted of PrP(C) [16]. These include roles in neuroprotection, synaptic integrity, neuronal excitability and memory formation. However, most of these observations have not been reproduced in subsequent studies, found little or no physiological or pathological correlates, or were later shown to arise from genetic impurities of the employed mouse models [17, 18]. In fact, a number of previous lines used to study the physiological function of PrP(C) were non-co-isogenic Prnp(-/-) mice, in some cases leading to artifactual conclusions [18]. Curiously, some of the clearest observations regarding PrP(C) function have been collected by studying the protein outside prion diseases. These include roles in the regulation of myelin homeostasis [19], immune processes [20] and in the progression of cancer [21]. Although it seems unlikely that a single protein could be involved in such a wide range of physiological processes, particularly in light of the relatively small number of phenotypic changes observed in PrP(C)-deficient mice, the lack of a clear understanding of the activity of this protein forces us to remain open minded. Thus, in this manuscript we review the most compelling data suggesting a putative role for PrP(C) beyond prion diseases and discuss potential therapeutic implications arising from such observations.

A role for PrP(C) in other neurodegenerative disorders

Despite the lack of consensus around the normal function(s) of PrP(C) in the central nervous system (CNS), misfolding of PrP(C) with accumulation of altered conformers (PrP(Sc)) in the brain is considered the fundamental pathogenic event in prion diseases [22, 23], with a potential role for PrP(C) in the development of other neurodegenerative diseases such as Alzheimer’s disease and the α-synucleinopathies increasingly described.

Alzheimer’s disease

In early studies predominantly relying on cell culture models, PrP(C) was described as favourably regulating the activity of β-secretase (β-site APP cleaving enzyme; BACE1), whereby production of neurotoxic Aβ peptides was reduced [24]. This reported capacity of PrP(C) appeared to require PrP(C) localisation in cholesterol-rich lipid rafts and the N-terminal polybasic region [24] thereby allowing direct interaction with Golgi-localised, immature forms of BACE1 causing trapping within the Golgi and reduced BACE1 levels at the cell surface and in endosomes [25]. Of interest, a mutant form of APP (carrying the Swedish mutation) was reported to escape this beneficial regulatory effect of PrP(C), in keeping with a potential protective effect for sporadic Alzheimer’s disease but probably not for at least some types of genetic Alzheimer’s disease. Unfortunately, the translational relevance and validity of these early observations has become less clear with the passage of time. In one follow-up study from the same laboratory, Whitehouse and colleagues reported that human brains demonstrated an ~50% reduction of PrP(C) expression in sporadic Alzheimer’s disease frontal cortex compared with age-matched controls, with PrP(C) levels inversely correlated with BACE1 activity, Aβ load, soluble Aβ levels and the Braak neurofibrillary tangle stage of disease [26]. In contrast however, a more recent report from this group, primarily utilising PrP(C) gene ablated (PrP(C0/0)) transgenic mice expressing wild-type human APP, the absence of PrP(C) appeared to have no effect on BACE1 activity, with levels of APP proteolytic fragments, cognate Aβ peptides and histopathological findings in the brains of these mice unaltered compared to controls [27]. Further potentially linking PrP(C) to the processing of APP and the generation of deleterious Aβ peptides, another group has reported that the genes influenced by the amyloid intracellular domain transcription regulation fragment produced through γ-secretase processing of β-APP includes the gene encoding PrP(C) (Prnp) through a p53-dependent pathway [28], possibly constituting a negative feedback loop. In a subsequent report employing a combination of experimental approaches, however, this putative role for the amyloid intracellular domain in influencing PrP(C) expression levels could not be reproduced, once again leaving uncertainty about the biological validity of the original observations [29]. Additional observations suggesting a potential neuroprotective effect of PrP(C) in Alzheimer’s disease have been provided by Rial and co-workers [30]. Utilising a mouse model centred on the effects of a single intracerebroventricular injection of 400 nmol of Aβ1-40 peptide on spatial learning and memory, these authors demonstrated reduced cognitive impairment in transgenic Tg-20 mice (that overexpress PrP(C) five-fold) compared with wild-type and transgenic PrP(C0/0) mice, with the Tg-20 mice also displaying less evidence of apoptosis and cell damage in the hippocampus. The mechanism of neuroprotection was not explored by the authors but other reports raise the possibility that glutamate excitotoxicity may be relevant with PrP(C) able to directly attenuate excessive N-methyl-D-aspartate receptor (NMDAR) activity in a copper-dependent manner, including that induced by the presence of Aβ1-42 peptide [31–33]. In contrast to any potential neuroprotective effects afforded by PrP(C) in Alzheimer’s disease, there is considerable evidence supporting a likely deleterious role in Alzheimer’s disease pathogenesis. PrP(C), through direct binding to residues 95-113, may act to disassemble amyloid fibrils composed of Aβ peptides thereby trapping constituent peptides into an oligomeric state effectively enriching the concentration of putative neurotoxic oligomers [34], but most evidence suggests the harmful behaviour of PrP(C) is through acting as a receptor to transduce the toxic signal of soluble Aβ peptides. Such deleterious effects of this PrP(C) mediated toxic signal transduction include impairment of hippocampal long-term potentiation (LTP), dendritic spine retraction and disruption of rodent spatial memory. In their seminal report, Lauren and co-workers exploited expression cloning to determine that PrP(C) binds with nanomolar affinity to soluble Aβ peptides (primarily through the charge cluster residues 95–110) subserving blockade of hippocampal slice LTP, with synaptic function rescued by anti-PrP antibodies [5]. Despite the inability of early follow-up reports to replicate this implicated pathogenic role for PrP(C) [35–37], subsequent reports have re-affirmed and elaborated this apparent crucial transduction role for mediating soluble Aβ oligomer toxicity. After Aβ oligomers bind PrP(C) at dendritic spines
(possibly also inhibiting constitutive endocytosis and causing clustering of PrPC on the cell surface [38]), the αβ oligomer-PrPC complex associates with Fyn causing activation of this Src kinase leading to tau hyperphosphorylation [39], as well as phosphorylation of the NR2B subunit of NMDARs. The kinase activity of Fyn on NMDARs culminates in depletion of these glutamatergic ion channels at the synaptic surface in parallel with loss of dendritic spines [40–42]. In addition to deleterious synaptic changes, axonal and neuronal loss are reported as downstream pathophysiological consequences of αβ oligomers binding to PrPC along with impairment of spatial learning and memory [43, 44]. As a sequitur to these various reports of the importance of PrPC as a key transducing mediator of soluble αβ neurotoxicity, anti-PrP antibodies primarily directed against an epitope within the oligomer binding site have been described as ameliorating or rescuing rodent hippocampal LTP and cognitive function [5, 45–48].

**Alpha-synucleinopathies**

Beyond a likely participation of PrPC in Alzheimer’s disease pathogenesis, the normal form of the prion protein has also recently been suggested to contribute to the pathogenesis of α-synucleinopathies, such as Parkinson’s disease and diffuse Lewy body disease, although discrepancies in findings across reports is noteworthy. Harnessing in vivo and in vitro models, Ferreira and colleagues reported a deleterious interaction of α-synuclein oligomers (but not α-synuclein monomers or fibrils) with PrPC at the NMDAR causing a failure of LTP in wild-type mouse hippocampal slices; this putative role for PrPC was supported by the abrogation of LTP impairment when utilising PrPC0/0 hippocampal slices [12]. Moreover, attempts to block the interaction of α-synuclein oligomers with PrPC using antibodies targeting specific PrPC amino acid segments revealed that the integrity of the 93–109 (charge cluster) region was necessary to observe such LTP impairment. The PrPC-mediated inhibition of synaptic plasticity was also prevented with the use of a specific Fyn inhibitor when co-incubated with the α-synuclein oligomers, suggesting that an interaction of the α-synuclein oligomer-PrPC complex promotes phosphorylation of the NMDAR through Fyn, thereby causing excessive Ca2+ influx at the post-synaptic terminal. The interaction between complexes of glycosylphosphatidyl-inositol (GPI)-anchored PrPC and α-synuclein oligomers with cytosolic Fyn appears possible through metabolotropic glutamate receptor 5 (mGlur5), as using specific inhibitors of mGlur5-mediated phosphorylation of NMDAR was also able to rescue LTP and cognitive deficits in these mice to levels equivalent to controls. Interestingly, an analogous molecular pathophysiological mechanism has also been observed in ex vivo and in vivo models of Alzheimer’s disease assessing synaptic impairment driven by soluble αβ oligomers, with blockade of the adenosine A2A receptors responsible for mGlur5 activation resulting in the inhibition of the deleterious NMDAR phosphorylation via Fyn [40, 41]. Apparently incongruous with the aforementioned study showing that PrPC selectively bound only to α-synuclein oligomers to subserve their detrimental effects, Aulić and co-workers reported that PrPC mediated the cellular uptake and spread of recombinant α-synuclein amyloid fibrils, with this activity attenuating the propagation of misfolded PrPC in vitro and in vivo scrapie infection models [11]. Although supporting a role for PrPC in mediating the movement of α-synuclein, another group suggested that although the pathological spreading of α-synuclein may be facilitated by PrPC, it is not exclusively dependent on PrPC [49]. Despite the reported inability of α-synuclein oligomers to induce LTP impairment in PrPC0/0 mouse hippocampal slices, the role of PrPC in directly mediating neurotoxicity and any direct interaction between α-synuclein oligomers and PrPC are still a matter of controversy. Employing a range of biophysical techniques to assess an intimate interaction between α-synuclein and PrPC, including surface plasmon resonance, La Vitola and colleagues were unable to confirm any direct association of PrPC with recombinant α-synuclein oligomers [50], as well as α-synuclein monomers and fibrils, although α-synuclein monomers appeared to suppress PrPC concatenation through inhibiting nucleation. In addition, La Vitola and colleagues observed that primary neuronal cultures derived from wild-type and PrPC0/0 mice were equally susceptible to α-synuclein oligomer neurotoxicity in a dose-dependent manner [46]. Finally, employing an in vivo model using intracerebroventricular injection of α-synuclein oligomers, they also reported that PrPC0/0 mice displayed similar memory deficits and hippocampal gliosis to wild-type controls. Although the influence of differences in methodology cannot be ruled out, these findings support the likelihood of α-synuclein oligomer mediated neurotoxicity independent from PrPC. Clearly, whereas any role of PrPC in non-prion neurodegenerative diseases remains incompletely understood and a subject of contention (especially in α-synucleinopathies), it appears likely that the normal form of the prion protein may play some part in these other diseases, which for Alzheimer’s disease may involve both protective and pathogenic contributions.

**PrPC in the immune system and related diseases**

Over the last few years the interest of immunologists in PrPC and immune diseases has vastly increased. Two main pieces of evidence may justify such interest: firstly, PrPC has extensively been studied in the central nervous system but is also widely expressed in cells of the immune system [51]; secondly, immune tolerance to PrPC has been documented [52–54]. Indeed, immune tolerance may prevent robust immune responses to prions; accordingly, PrP-specific antibodies have not been detected in animals infected with prions. In addition, other studies reported that the immune system may also actively contribute to prion disease pathogenesis, by amplifying prion load in lymphoid compartments, transferring the pathogenic PrPSc to cells and facilitating efficient neuroinvasion [20, 52]. Although it is clear that components of the immune system can contribute to the spread of prions, none of these pieces of evidence have been extensively validated at the molecular level, and conflicting results have often been reported [20, 55]. Overall, based on these observations, two specific roles of the immune system in prion diseases can be identified: immune cells may perform, when properly activated, as a protective shield against prions but, at the same time, they may be involved in the accumulation and spreading of pathogenic PrPSc [56]. For these reasons, manipulation
of the immune system has been envisioned as a potential therapeutic option for prion diseases [57]. Immunotherapies have reported promising results in vitro and in vivo. In particular, three main approaches have been undertaken so far: (i) treatment with antibodies targeting PrPSc [58–61]; (ii) vaccines with antigen-loaded dendritic cells [62, 63]; and (iii) adoptive transfer of PrP-specific CD4+ T lymphocytes [64]. Although more research into mechanism and safety of these approaches is still required, these immunotherapies may offer potential novel tools to clear the pathological form of PrP. However, because the function of cellular PrP in the lymphoid system and in the CNS remains to be fully elucidated, it is not yet clear how therapies targeting PrPSc, which shows similarities with PrPβ, will affect immune or other specific endogenous functions. For this reason, uncovering the role of PrPβ in cells of the immune system may provide novel insights both into its role in the pathogenesis of prion diseases and in specific functions of immune cells in general.

**PrPβ in immune cells: expression and functions**

Its high evolutionary conservation suggests that PrPβ fulfills ancient and still essential biological functions [65–67]. Notably, PrPβ is abundantly expressed in neural cells, including neurons and glia [68], as well as in subsets of cells of haematopoietic origin (e.g., myeloid dendritic cells, DCs, and T cells) [69]. In particular, data suggest that PrPβ is involved in specific immune functions, including T cell development, DC activation, inhibition of macrophage phagocytosis and immunological quiescence [70, 71]. In addition to DCs and T cells, PrPβ has been detected also in B lymphocytes, natural killer cells, platelets, monocytes and in follicular DCs [72–75]. Within lymphoid cells, B cells express lower levels of PrPβ compared with T cells and natural killer cells [76]. In addition, it has long been known that PrPβ is present on the surface of lymphocytes and it is rapidly upregulated upon their activation [77]. Following T cell activation, PrPβ is redistributed in specific structures such as lipid rafts, together with signalling molecules, leading to immunomodulation [78]. It has been shown that GPI-anchored PrPβ is enriched at the immunological synapse and can interact with components of the T cell receptor, such as the Fyn tyrosine kinase and the zeta chain-associated protein kinase 70 (ZAP-70), leading to the modulation of T cell receptor signalling cascade [75, 77, 79]. Moreover, PrPβ expression was reported to be higher in T cells than in B lymphocytes, with CD8+ cell subsets expressing slightly more PrPβ than CD4+ cells [76, 80]. PrPβ expression is also higher in CD45RO+ memory compared with CD45RA+ naive T lymphocytes [75, 81]. Interestingly, data from gene arrays have revealed the murine Prnp gene to be up-regulated in T cell [82], via a Stat6-dependent mechanism, during interleukin (IL)-4 driven Th2 differentiation [83] and in CD8+ memory T cells [84]. In addition, it has been reported that regulatory CD4+ CD25+ T cells (Tregs) expressed 4.5 fold higher levels of PrPβ messenger RNA and showed a 10-fold higher intensity of surface PrPβ than effector CD4+ CD25− T cells, despite no loss-of-function phenotypes could be recognised in Treg cells from Prnp−/− mice [85]. Hence, PrPβ may be more important in certain types of functionally differentiated lymphocytes that operate in particular immune environments. Outside the nervous system, the antigen-presenting cells, DCs display the highest expression levels of PrPβ, in both humans and mice [69, 86]. Studies on myeloid DCs showed that PrPβ levels particularly increase during differentiation and maturation of these cells, in parallel with molecules involved in antigen presentation, such as major histocompatibility complex type II (MHC-II) and costimulatory molecules [69]. Interestingly, it has been demonstrated that important differences of PrPβ expression exist between different DC subpopulations either analysed after ex vivo isolation or differentiated in vitro. DCs can be classified in two major categories: conventional DCs (cDCs), which include at least two different DC subsets (e.g., cDC1 and cDC2) and plasmacytoid DCs (pDCs) [87, 88]. PrPβ was found on the surface of bone marrow-derived human and mouse conventional DCs generated in vitro or isolated from the spleen, but not in pDCs [88]. PrPβ expression in these cDCs was strongly up-regulated after maturation by TLR ligands, such as bacterial lipopolysaccharide and CpG. Interestingly, a study from Ballerini et al. showed that membrane PrPβ on DCs enhanced the stimulation of specific naïve T cells both in vitro and in vivo [89]. High expression of PrPβ was also found on the surface of CD8+ cDC subset, both in the spleen and the lymph-nodes [88]. Although the different PrPβ expression between cDCs and pDCs could be related to the specific developmental programme of these two cell types, the specific role of PrPβ in cDC functions still remains to be explored. Related to these issues, specific evidence suggests that absence of PrPβ in T cells and DCs had different outcomes in T-cell proliferation. Specifically, T cells devoid of PrPβ exhibited a normal alloregenic antigen response, while DCs lacking PrPβ significantly reduced proliferation of interacting T cells, suggesting that PrPβ might serve different signalling roles in the two cell types [90]. Another class of dendritic cells, the follicular dendritic cells (FDCs), express high levels of the PrPβ, although its function in these cells is still uncertain. In fact, it has been shown that PrPβ is dispensable for the maturation of FDCs and for maintaining antigen-specific antibody responses [91]. PrPβ has also been found in macrophages and its expression is associated with both the inflammatory M1 phenotypes and with the immunosuppressive M2 types. Interestingly, recent studies have demonstrated that PrPβ mice produce reduced amounts of the anti-inflammatory cytokine IL-10 in response to systemic lipopolysaccharide, potentially suggesting a role for PrPβ in promoting IL-10 production in M2 macrophages [92]. Moreover, again in macrophages, it has been demonstrated that PrPβ plays important role in phagocytosis [93, 94]. In particular, Wang and colleagues demonstrated that mouse bone marrow-derived macrophages infected with Escherichia coli express high levels of Prnp mRNA, leading to inefficient phagocytosis. Conversely, macrophages devoid of PrPβ internalised bacteria and increased the expression of cytokines such as interleukin-1β, decreasing bacterial proliferation [95]. These data reveal a potentially important role of PrPβ as a negative regulator of phagocytosis, phagosome maturation, cytokine expression, and macrophage microbiocidal activity. Further studies are required to determine how PrPβ regulates vesicular trafficking associated with phagocytosis and cytokine secretion.
Review article: Biomedical intelligence

PrP	extsuperscript{C} in immune disorders

The role of PrP	extsuperscript{C} in health and homeostatic cell functions is still obscure, but several potential roles have been attributed to this protein in the immune system. Specifically, several studies suggest that PrP	extsuperscript{C} may act as a modulator of innate immune responses in pathologies beyond prion diseases [96–98]. The detailed molecular means by which PrP	extsuperscript{C} modulates immune signalling pathways contributing to immune modulation are not yet clarified and stand out as a necessary area of future research. Interestingly, PrP	extsuperscript{C} is expressed in various organs that, by multiple mechanisms, are relatively protected from inflammation (i.e., immunoprivated sites) such as the brain, eye, placenta, the pregnant uterus and testes [99, 100]. This high expression in immuno-privileged organs suggest that PrP	extsuperscript{C} has an important protective role under inflammatory stress and/or tissue damage [90, 101]. Accordingly, specific reports have shown that the absence of PrP	extsuperscript{C} increases inflammatory damage in different models of inflammation such as experimental brain ischaemia, brain trauma and experimental autoimmune encephalomyelitis [102]. For example, experimental autoimmune encephalomyelitis, the animal model for human multiple sclerosis, is worsened in mice lacking PrP	extsuperscript{C}. In particular, in the acute stage, the spinal cords, cerebellums and forebrains of Prnp-/- deficient mice were shown to be more heavily infiltrated with leukocytes and exhibited stronger pro-inflammatory cytokine gene expression, as compared with those seen in wild-type mice. Remarkably, the persistence of leukocyte infiltration in the forebrain and cerebellum was accompanied by increased pathogenic cytokines, such as interferon (IFN)-γ and IL-17 [103]. In this particular model, disease exacerbation has been attributed to T cells that would differentiate into more inflammatory (i.e., Th1 and Th17) and behave more aggressively against the CNS effectors, when deprived of PrP	extsuperscript{C} [104]. Thus, based on these results, attenuation of T cell-dependent neuroinflammation may represent a potential novel function of PrP	extsuperscript{C}. In addition to experimental autoimmune encephalomyelitis, PrP	extsuperscript{C} also appears to be protective in autoimmune colitis. Inflammatory bowel disease, induced by dextran sodium sulphate (DSS), is more severe in PrP	extsuperscript{C}−/− mice than in wild-type mice. Accordingly, overexpression of PrP	extsuperscript{C} greatly attenuates DSS-induced colitis [105]. Again, depletion of PrP	extsuperscript{C} was able to skew T cells toward more pronounced Th1 and Th17 inflammatory phenotypes [79]. Based on these data, variations in the human PRNP gene or its sequence [106] might have effects on disease susceptibility or the clinical course of autoimmune diseases; however, these specific studies have not yet been performed. Another interesting observation is that PrP	extsuperscript{C} may act as antimicrobial peptide. It was demonstrated that synthetic peptides derived from the N-terminal region of PrP	extsuperscript{C} are cytotoxic to several bacterial species, including E. coli, Pseudomonas aeruginosa, Bacillus subtilis and Staphylococcus aureus [107]. In addition, in 2013 Ding and co-workers showed that PrP	extsuperscript{C} participates in the regulation of microglial response to Mycobacterium bovis infection, through the upregulation of pro-inflammatory cytokines and the modulation of apoptosis [108]. In particular, they found a significant increase of Prnp mRNA expression upon microglial cell infection with M. bovis, and Prnp silencing did not alter the expression pattern of anti-inflammatory cytokines IL-10 and transforming growth factor (TGF)-β. PrP	extsuperscript{C} was also shown to possess antiviral properties by inhibiting the replication of the human immunodeficiency virus type 1 (HIV-1) and the murine leukaemia virus [109]. In these studies, PrP	extsuperscript{C} was able to bind the viral genomic RNA of HIV-1 negatively affecting its translation. Moreover, PrP	extsuperscript{C} was found to co-localise with the virus assembly machinery at the plasma membrane and at the virological synapse in infected T cells. Depletion of PrP	extsuperscript{C} in infected T cells and microglia favoured HIV-1 replication [109]. Within this conceptual framework, it has been suggested that PrP	extsuperscript{C} may serve two principal roles in immune system: to modulate the inflammatory potential of immune cells, and to protect vulnerable parenchymal cells against noxious insults generated through inflammation. The mechanisms lying behind the role of PrP	extsuperscript{C} and their significance for pathogenesis and its regulatory roles in specific immune disorders require further investigation.

PrP	extsuperscript{C} and cancer

The first hint of a link between PrP	extsuperscript{C} and cancer dates back to the early 2000s when PRNP was identified as one of the 30 genes most overexpressed in pancreatic cancer cell lines as compared with normal cells [110]. At the same time, PrP	extsuperscript{C} was reported to be upregulated in a drug-resistant gastric cancer cell line as compared with the parental cell line [111]. That elevated PrP	extsuperscript{C} may confer resistance to anticancer agents was soon confirmed by Diarra-Mehrpour and colleagues, who demonstrated a causal relationship between increased PrP	extsuperscript{C} expression and resistance to tumour necrosis factor-α (TNFα) in a breast cancer cell line [112]. Thereafter, de Wit and colleagues came across PrP	extsuperscript{C} when screening for cell surface molecules associated with adenoma to carcinoma transition in colon cancer [113]. Following these pioneering findings, further studies have consolidated the involvement of PrP	extsuperscript{C} in four main aspects of cancer biology: proliferation; resistance to anticancer agents; cell migration and invasion; and epithelial to mesenchymal transition. More recently, links between PrP	extsuperscript{C} and cancer stem cells (CSCs) (see below), as well as aneuploidy, were also uncovered [114]. Furthermore, although scarce, studies featuring patients globally point to an association between high PrP	extsuperscript{C} expression and poor prognosis [115–120]. It is now well established that PrP	extsuperscript{C} may sustain cancer cell proliferation in various types of cancers: gastric [121], pancreatic [120] and colon cancer [116, 122, 123], as well as glioblastoma [117, 124] and schwannoma [125]. From a mechanistic point of view, PrP	extsuperscript{C} was shown to promote the recruitment of a P13 kinase (PI3K)-AKT pathway, itself controlling the transcription of CyclinD1 in gastric cancer cells [121] and to activate the MAP kinases ERK1/2 upon interaction with the STI1 chaperone in glioblastoma [117, 126]. In pancreatic cancer cells, the pro-proliferative action of PrP	extsuperscript{C} appears to involve activation of the Notch pathway [127]. Moreover, the capacity of PrP	extsuperscript{C} to sustain cell proliferation in colon cancer cells may relate to enhanced glucose uptake, as PrP	extsuperscript{C}-dependent signalling leads to transcription of the GLUT1 gene [123]. Overall, the contribution of PrP	extsuperscript{C} to cancer cell proliferation fully fits with a gain of its physiological function in normal cells where it controls the activation of several effectors associated with cell growth [128, 129].
A second field of investigation focuses on the correlation between PrPC and chemo-resistance. High PrPC expression levels is indeed associated with increased resistance to various types of agents in glioblastoma [130], gastric [111, 121, 131, 132], breast [112, 133–135], and colon cancer [122, 136, 137]. According to several studies, the PrPC-PI3K-AKT pathway could contribute to drug resistance by enhancing the expression of MDR1 (multidrug-resistance protein 1) [138]. Very recently, PrPC was found to confer resistance to doxorubicin in breast cancer cells by directly binding and sequestering the drug via its N-terminal domain [119]. Consistently, the authors found a significant correlation between PRNP gene expression levels and resistance to treatment in breast cancer patients, arguing that PRNP monitoring could help stratify patients for adequate therapy. A third process to which PrPC takes part in cancer cells is invasion/migration. Elevated PrPC was shown to confer enhanced migratory and/or invasive properties to glioblastoma [126], gastric [118], breast [133, 139], pancreas [127], colon [140] lung [141] and melanoma [142] cell lines. In pancreatic cancer and melanoma, PrPC, which is present as pro-PrP (an isoform retaining its C-terminus instead of a GPI anchor), appears to exert its pro-migratory action by interacting with filamin A, itself connected with the actin cytoskeleton [142, 143]. In colon cancer cells, this is triggered by the binding of PrPC with its ligand STI1 [140]. Of note, the pro-invasive and pro-migratory role of PrPC extends to the in vivo situation in animal models. Indeed, Du and colleagues found that among colon primary tumour cells, only those positive for PrPC were able to promote liver metastasis after injection in the caecal wall of immunocompromised mice [115]. Whether this holds true for other types of cancer remains to be investigated.

Metastatic dissemination is highly correlated with epithelial-to-mesenchymal transition (EMT), a process whereby cells lose epithelial markers and cell-cell and cell-matrix contacts, remodel their actin cytoskeleton and acquire mesenchymal hallmarks, favouring cell migration [144]. At a molecular level, EMT induction is controlled by various transcription factors, including ZEB1, ZEB2, SNAIL, SLUG and TWIST [144]. The expression of PRNP is highly associated with and EMT signature in colon cancer patients, and PrPC controls the expression of ZEB1 in colon cancer cells [116]. Interestingly, EMT appears to be intimately connected with CSC properties [145]. Accordingly, Du and colleagues documented that PrPC-positive primary colon cancer cells express high levels of the EMT-associated markers TWIST and N-cadherin and low levels of the epithelial marker E-cadherin and exhibit CSC properties such as expression of the CSC marker CD44 and tumour-initiating capacity [115]. In line with this, PrPC was shown to interact with CD44 in multi-resistant breast cancer cells [133]. Furthermore, in primary glioblastoma cells, PrPC silencing reduces the expression of the EMT-associated markers TWIST and N-cadherin and low levels of the epithelial marker E-cadherin and exhibit CSC properties such as expression of the CSC marker CD44 and tumour-initiating capacity [115]. In line with this, PrPC was shown to interact with CD44 in multi-resistant breast cancer cells [133]. Furthermore, in primary glioblastoma cells, PrPC silencing reduces the expression of the EMT-associated markers TWIST and N-cadherin and low levels of the epithelial marker E-cadherin and exhibit CSC properties such as expression of the CSC marker CD44 and tumour-initiating capacity [115]. In line with this, PrPC was shown to interact with CD44 in multi-resistant breast cancer cells [133]. Furthermore, in primary glioblastoma cells, PrPC silencing reduces the expression of the EMT-associated markers TWIST and N-cadherin and low levels of the epithelial marker E-cadherin and exhibit CSC properties such as expression of the CSC marker CD44 and tumour-initiating capacity [115]. In line with this, PrPC was shown to interact with CD44 in multi-resistant breast cancer cells [133]. Furthermore, in primary glioblastoma cells, PrPC silencing reduces the expression of the EMT-associated markers TWIST and N-cadherin and low levels of the epithelial marker E-cadherin and exhibit CSC properties such as expression of the CSC marker CD44 and tumour-initiating capacity [115].
as neurospheres [126]. As with proliferation, the contribution of PrPC to CSC self-renewal may be envisioned as a diversion of its physiological role in normal stem cell maintenance [146]. Collectively, the involvement of PrPC in various aspects of cancer progression may be viewed as directly related to its physiological role in normal cells. From a therapeutic perspective, reducing PrPC expression through antisense oligonucleotide-based strategies [147] may prove beneficial, as documented for glioblastoma [148] or colon cancer [115]. Besides, alternative opportunities may ensue from a better knowledge of the signals upregulating PrPC expression in cancer cells.

Conclusions

After more than three decades of intense research across numerous research laboratories around the planet there is still much to learn about the biology of PrP [10]. A large amount of data provides solid experimental support for the notion that the simple accumulation of PrPC in nerve tissues may not explain the whole spectrum of neurotoxic events occurring in prion diseases, which instead is likely to require some poorly understood subversion of PrPC function upon binding to PrPC [9]. Such a role for corruption of PrPC as a mediator of prion toxicity has received unexpected support from research in other neurodegenerative disorders, showing that PrPC can bind disease-associated misfolded proteins, such as oligomers of Aβ and alpha-synuclein. Research in even more distant fields of biology supports expanded and surprising roles for PrPC in several physiological and disease contexts outside the brain, such as myelin homeostasis, immunoregulatory processes and cancer (figure 1). These approaches, which might not appear directly relevant to prion biology and patho-biology, are nevertheless laying the groundwork for a more comprehensive understanding of the physiological function(s) of PrP, and the likelihood of achieving novel insights that could elucidate some fundamental cytotoxic mechanisms potentially shared by prion disorders and several other diseases.

Financial disclosure

This work was supported by a grant from Fondazione Telethon (Italy, TCF14009).

Potential competing interests

GS is a recipient of a fellowship from Fondazione Telethon. EB is an Assistant Teacher Scientist at the Dulbecco Telethon Institute. SJC is funded in part by a NHMRC Practitioner Fellowship (identification #APP1105784). FF is funded by Italian Foundation multiple sclerosis 2019/12-single/012.

References

1. Chiti F, Dobson CM. Protein Misfolding. Amyloid Formation, and Human Disease: A Summary of Progress Over the Last Decade. Annu Rev Biochem. 2017;86(1):27–68. doi: http://dx.doi.org/10.1146/annurev-biochem-061516-045115, PubMed.

2. Powell T. Health Policy and Dementia. Curr Psychiatry Rep. 2018;20(1):4. doi: http://dx.doi.org/10.1007/s11920-018-0868-0, PubMed.

3. Selkoe DJ, Hardy J. The amyloid hypothesis of Alzheimer’s disease at 25 years. EMBO Mol Med. 2016;8(6):595–608. doi: http://dx.doi.org/10.15252/emmm.2016060210, PubMed.

4. Walsh DM, Klysbin I, Faddeeva JV, Cullen WK, Anwyl R, Wolfe MS, et al. Naturally secreted oligomers of amyloid beta protein potently inhibit hippocampal long-term potentiation in vivo. Nature. 2002;416(6880):535–9. doi: http://dx.doi.org/10.1038/416553a, PubMed.

5. Lauren J, Gimbel DA, Nygaard HB, Gilbert JW, Strittmatter SM. Cellular prion protein mediates impairment of synaptic plasticity by amyloid-beta oligomers. Nature. 2009;457(7233):1128–32. doi: http://dx.doi.org/10.1038/nature07761, PubMed.

6. Prusiner SB. Prions. Proc Natl Acad Sci USA. 1989;85(23):13383–8. doi: http://dx.doi.org/10.1073/pnas.85.23.13384, PubMed.

7. Aguzzi A, Heikenwalder M, Polymeren M. Insights into prion strains and neurotoxicity. Nat Rev Mol Cell Biol. 2007;8(7):552–61. doi: http://dx.doi.org/10.1038/nrm2204, PubMed.

8. Brandner S, Iennuzzi S, Rauber A, Fischer M, Sailer A, Kobayashi Y, et al. Normal host prion protein necessary for scrapie-induced neurotoxicity. Nature. 1996;379(6563):339–43. doi: http://dx.doi.org/10.1038/379396a0, PubMed.

9. Brandner S, Rauber A, Sailer, Blüthner T, Fischer M, Weissmann C, et al. Normal host prion protein (PrPc) is required for scrapie spread within the central nervous system. Proc Natl Acad Sci USA. 1996;93(23):13148–51. doi: http://dx.doi.org/10.1073/pnas.93.23.13148, PubMed.

10. Malucci C, Dickinson A, Linehan J, Klöhn PC, Brandner S, Collinge J. Depleting neuronal PrP in prion infection prevents disease and reverses spongiosis. Science. 2003;302(5646):871–4. doi: http://dx.doi.org/10.1126/science.1090187, PubMed.

11. Antúl S, Maspero L, NaKaKiewicz J, Isopi E, Bistafi E, Ambrosetti E, et al. α-Synuclein Amyloid Hijack Prion Protein to Gain Cell Entry, Facilitate Cell-to-Cell Spreading and Block Prion Replication. Sci Rep. 2017;7(1):10050. doi: http://dx.doi.org/10.1038/s41598-017-10236-x, PubMed.

12. Ferreira DG, Tomido-Ferreira M, Vicente Miranda H, Batalla VL, Coelho JE, Szégo ÉM, et al. α-synuclein interacts with PrPc to induce cognitive impairment through mGluR5 and NMDAR2B. Nat Neurosci. 2017;20(11):1569–79. doi: http://dx.doi.org/10.1038/nmn.4468, PubMed.

13. Resenberger UK, Winklhofer KF, Tatzi F. Cellular prion protein mediates toxic signaling of amyloid beta. Neurodegener Dis. 2012;10(1):298–300. doi: http://dx.doi.org/10.1159/000332596, PubMed.

14. Corbet GT, Wang Z, Song W, Colom-Cadena M, Rose J, Liao M, et al. PrPc is a central player in toxicity mediated by soluble aggregates of neurodegeneration-causing proteins. Science. 2010;330(6008):103–26. doi: http://dx.doi.org/10.1126/science.1196019, PubMed.

15. Biasini E, Turnbaugh JA, Unterberger U, Harris DA. Prion protein at the crossroads of physiology and disease. Trends Neurosci. 2012;35(9):281–93. doi: http://dx.doi.org/10.1016/j.tins.2011.10.002, PubMed.

16. Linden R. The Biological Function of the Prion Protein: A Cell Surface Scaffold of Signaling Modules. Front Mol Neurosci. 2017;10:77. doi: http://dx.doi.org/10.3389/fnmol.2017.00077, PubMed.

17. Nuvolone M, Hermann M, Sorso S, Russo G, Tiberi C, Schwartz P, et al. Strictly co-isogenic C57BL/6J-PrpC–/– mice: A rigorous resource for prion science. J Exp Med. 2016;213(3):313–27. doi: http://dx.doi.org/10.1084/jem.20151610, PubMed.

18. Wolf MA, سنatore A, Aguzzi A. The biological function of the cellular prion protein: an update. BMC Biol. 2017;15(1):34. doi: http://dx.doi.org/10.1186/s12915-017-0375-5, PubMed.

19. Küffner A, Lakkaraju AK, Mogha A, Petersen SC, Airich K, Doucereau C, et al. The prion protein is an agonistic ligand of the G protein-coupled receptor Adgrg6. Nature. 2017;543(7617):464–8. doi: http://dx.doi.org/10.1038/nature19312, PubMed.

20. Mabbott NA. Immunology of Prion Protein and Prions. Prog Mol Biol Transl Sci. 2017;150:203–40. doi: http://dx.doi.org/10.1016/bs.pmbts.2017.06.004, PubMed.

21. Hirsch TZ, Martin-Lamorte S, Mouillet-Richard S. Functions of the Prion Protein. Prog Mol Biol Transl Sci. 2017;150:1–34. doi: http://dx.doi.org/10.1016/bs.pmbts.2017.06.001, PubMed.

22. Chesebro B, Race R, Wehry K, Nishio J, Bloom L, Lechner D, et al. Identification of scrapie prion protein-specific mRNA in scrapie-infected and uninfected brain. Nature. 1985;316(6017):331–3. doi: http://dx.doi.org/10.1038/315333a0, PubMed.

23. Prusiner SB. Novel proteinaceous infectious particles cause scrapie. Science. 1982;216(4542):136–44. doi: http://dx.doi.org/10.1126/science.6801762, PubMed.

24. Parkin ET, Want NT, Hussain I, Eckman EA, Eckman CB, Manson JC, et al. Cellular prion protein regulates beta-secretase cleavage of the Alzheimer’s amyloid precursor protein. Proc Natl Acad Sci USA. 2007;104(26):11062–7. doi: http://dx.doi.org/10.1073/pnas.0609621104, PubMed.

25. Griffiths HH, Whitehouse JJ, Baybutt H, Brown D, Kellett KA, Jackson CD, et al. Prion protein interacts with BACE1 protein and differentially regulates its activity toward wild type and Swedish mutant amyloid pre-
prion protein expression is not regulated by the Alzheimer’s long precursor protein intracellular domain. PLoS One. 2012;7(2): doi: http://dx.doi.org/10.1371/journal.pone.0031754. PubMed.

36 Kheshtkhah M, Hozami H, Omid SM, Zare M, Maleki H. Prion protein affects cell cycle checkpoints of the human glioma cells. Brain Res Bull. 2011;87(3):172–177. doi: http://dx.doi.org/10.1016/j.brainresbull.2011.09.008. PubMed.

37 Kretschmer C, Jung C, Schmitz T, Seipel Y, Wawrzeniak K, Schebitz GR, et al. Impaired neuronal cell death and intracellular PrP accumulation in PrP-null mice after ischemia. Acta Neuropathol. 2011;121(1):103–114. doi: http://dx.doi.org/10.1007/s00401-010-0900-x. PubMed.

38 Kühn A, Stahl S, Buchholz D, Buck S, Diak P, Fluharty P, et al. Antiprion immunotherapy: to suppress or to eradicate prion disease? Exp Ther Med. 2014;8(3):535–544. doi: http://dx.doi.org/10.3892/etm.2014.1661. PubMed.

39 Kuo W, Lee HP, Zou WQ, Wang X, Perry G, Zhu X, et al. Cellular prion protein is essential for oligomeric amyloid-β-induced neuronal cell death. J Neurosci. 2010;30(18):5567–5576. doi: http://dx.doi.org/10.1523/JNEUROSCI.0935-10.2010. PubMed.

40 Kuo W, Lee HP, Zou WQ, Wang X, Perry G, Zhu X, et al. Cellular prion protein is essential for oligomeric amyloid-β-induced neuronal cell death. J Neurosci. 2010;30(18):5567–5576. doi: http://dx.doi.org/10.1523/JNEUROSCI.0935-10.2010. PubMed.

41 Kuo W, Lee HP, Zou WQ, Wang X, Perry G, Zhu X, et al. Cellular prion protein is essential for oligomeric amyloid-β-induced neuronal cell death. J Neurosci. 2010;30(18):5567–5576. doi: http://dx.doi.org/10.1523/JNEUROSCI.0935-10.2010. PubMed.

42 Kuo W, Lee HP, Zou WQ, Wang X, Perry G, Zhu X, et al. Cellular prion protein is essential for oligomeric amyloid-β-induced neuronal cell death. J Neurosci. 2010;30(18):5567–5576. doi: http://dx.doi.org/10.1523/JNEUROSCI.0935-10.2010. PubMed.

43 Kuo W, Lee HP, Zou WQ, Wang X, Perry G, Zhu X, et al. Cellular prion protein is essential for oligomeric amyloid-β-induced neuronal cell death. J Neurosci. 2010;30(18):5567–5576. doi: http://dx.doi.org/10.1523/JNEUROSCI.0935-10.2010. PubMed.

44 Kuo W, Lee HP, Zou WQ, Wang X, Perry G, Zhu X, et al. Cellular prion protein is essential for oligomeric amyloid-β-induced neuronal cell death. J Neurosci. 2010;30(18):5567–5576. doi: http://dx.doi.org/10.1523/JNEUROSCI.0935-10.2010. PubMed.

45 Kuo W, Lee HP, Zou WQ, Wang X, Perry G, Zhu X, et al. Cellular prion protein is essential for oligomeric amyloid-β-induced neuronal cell death. J Neurosci. 2010;30(18):5567–5576. doi: http://dx.doi.org/10.1523/JNEUROSCI.0935-10.2010. PubMed.
The cellular prion protein modulates phagocytosis and inflammation. J Immunol. 1998;160(5):2346–46. doi: http://dx.doi.org/10.1169/jimm.1998.160.5.2346.

McDade AC, Brown KL, Mahbott NA. Ablation of the cellular prion protein, PrPC, specifically on follicular dendritic cells has no effect on their maturation or function. Immunology. 2013;138(3):246–57. doi: http://dx.doi.org/10.1111/imn.12011.

Liu J, Zhao D, Liu C, Ding T, Yang L, Yin X, et al. Protein particulate in the protection of mice from lipopolysaccharide infection by regulating the inflammatory processes. J Mol Neurosci. 2015;55(2):279–87. doi: http://dx.doi.org/10.1007/s12031-014-0319-2.

de Almeida CJ, Chiarini LB, da Silva JP, E Silva PM, Martin MA, Linen D. The cellular prion protein modulates phagocytosis and inflammatory response. J Leukoc Biol. 2005;77(2):23–46. doi: http://dx.doi.org/10.1189/jlb.1105351.

Uraki R, Sakudo A, Ando S, Kitani H, Onoseda T. Enhancement of phagocytic activity by prion protein in PrP-deficient macrophages. Int J Mol Med. 2010;26(2):32–36. doi: http://dx.doi.org/10.3892/ijmm.2010.461.

Wang M, Zhao D, Yang Y, Liu J, Wang J, Yin X, et al. The cellular prion protein negatively regulates phagocytosis and cytokine expression in murine bone marrow-derived macrophages. PLoS One. 2014;9(7): doi: http://dx.doi.org/10.1371/journal.pone.0102785.

McDade SM, Prion protein: a pattern recognition receptor for viral components and uric acid responsible for the induction of innate and adaptive immunity. Med Hypotheses. 2005;65(3):570–7. doi: http://dx.doi.org/10.1016/j.mehy.2005.02.038.

Obst J, Simon E, Marcuso R, Gomez-Nicola D. The Role of Microglia in Prion Diseases: A Paradigm of Functional Diversity. Front Aging Neurosci. 2017;9:207. doi: http://dx.doi.org/10.3389/fnagi.2017.00207.

Dervishi E, Lam TH, Dunn SM, Zwierszewski G, Saleem F, Wishart DS, et al. Recombinant mouse prion protein alone or in combination with lipopolysaccharide alters expression of innate immune genes in the colon of mice. PLoS Pathog. 2015;11(9):95. doi: http://dx.doi.org/10.1371/journal.ppat.1005694.

Johnson ML, Graziul-Bilska AT, Reynolds LP, Redmer DA. Prion (PrPc) expression in ovariectomized uteri increases after estrogen treatment of ovariectomized and during early pregnancy. Reproduction. 2014;148(1):11–10. doi: http://dx.doi.org/10.1530/REP-13-0548.

Tani K, Saeki K, Matsumoto Y, Takeda M, Hirasewa K, Doi K, et al. Analysis of intracellular prion protein mRNA in brain of mice by in situ hybridization in brain, placenta, uterus and testis of rats. Int J Dev Biol. 1995;39(6):309–15. doi: http://dx.doi.org/10.1017/S0075165095000314.

Salvesen O, Reiten MR, Essvesen A, Bakkevik MK, Tranulis MA, Ersdal C. LPS-induced systemic inflammation reveals an immunomodulatory role for effector prion protein in the blood-brain interface. J Neuroinflammation. 2017;14(1):106. doi: http://dx.doi.org/10.1186/s12974-017-0879-5.

10.1046/j.1362-3109.1996.103198.x.

10.1046/j.1362-3109.1999.16185-x.

10.1046/j.1362-3109.1999.16192.x.

10.1046/j.1362-3109.1999.16193.x.

10.1046/j.1362-3109.1999.16194.x.

10.1046/j.1362-3109.1999.16195.x.

10.1046/j.1362-3109.1999.16196.x.

10.1046/j.1362-3109.1999.16197.x.

10.1046/j.1362-3109.1999.16198.x.

10.1046/j.1362-3109.1999.16199.x.

10.1046/j.1362-3109.1999.16200.x.

10.1046/j.1362-3109.1999.16201.x.

10.1046/j.1362-3109.1999.16202.x.

10.1046/j.1362-3109.1999.16203.x.

10.1046/j.1362-3109.1999.16204.x.

10.1046/j.1362-3109.1999.16205.x.

10.1046/j.1362-3109.1999.16206.x.

10.1046/j.1362-3109.1999.16207.x.

10.1046/j.1362-3109.1999.16208.x.

10.1046/j.1362-3109.1999.16209.x.

10.1046/j.1362-3109.1999.16210.x.

10.1046/j.1362-3109.1999.16211.x.

10.1046/j.1362-3109.1999.16212.x.

10.1046/j.1362-3109.1999.16213.x.
Promotes invasion and metastasis of gastric cancer

PrPc/par-4 interaction promotes the survival of human glioma cells

Prion protein promotes glutamate uptake through the Fyn-HiF2–Za-Ghirl pathway to support colorectal cancer

Promotes overall survival

Stem cell research in colorectal cancer

Biomedical intelligence

Swiss Med Wkly. 2020;150:w20222

Review article: Biomedical intelligence
137 Park JY, Jeong JK, Lee JH, Moon JM, Kim SW, Lee YJ, et al. Induction of cellular prion protein (PrPc) under hypoxia inhibits apoptosis caused by TRAIL treatment. Oncotarget. 2015;6(7):5342–53. doi: http://dx.doi.org/10.18632/oncotarget.3028. PubMed.

138 Liang J, Ge F, Guo C, Luo G, Wang X, Han G, et al. Inhibition of PI3K/Akt partially leads to the inhibition of PrP(C)-induced drug resistance in gastric cancer cells. FEBS J. 2009;276(3):685–94. doi: http://dx.doi.org/10.1111/j.1742-4658.2008.06816.x. PubMed.

139 Gil M, Kim YK, Kim KE, Kim W, Park CS, Lee KJ. Cellular prion protein regulates invasion and migration of breast cancer cells through MMP-9 activity. Biochem Biophys Res Commun. 2016;470(1):213–9. doi: http://dx.doi.org/10.1016/j.bbrc.2016.01.038. PubMed.

140 de Lacerda TC, Costa-Silva B, Giudice FS, Dias MV, de Oliveira GP, Teixeira BL, et al. Prion protein binding to HOP modulates the migration and invasion of colorectal cancer cells. Clin Exp Metastasis. 2016;33(5):441–51. doi: http://dx.doi.org/10.1007/s10683-016-9788-8. PubMed.

141 Lin SC, Lin CH, Shih NC, Liu HL, Wang WC, Lin KY, et al. Cellular prion protein transcriptionally regulated by NFIL3 enhances lung cancer cell lamellipodium formation and migration through JNK signaling. Oncogene. 2020;39(2):385–98. doi: http://dx.doi.org/10.1038/s41388-019-0994-0. PubMed.

142 Li G, Yu S, Nakamura F, Pentikäinen OT, Singh N, Yin S, et al. Pr-protein binds filamin A, facilitating its interaction with integrin beta1, and contributes to melanomagenesis. J Biol Chem. 2010;285(39):30328–39. doi: http://dx.doi.org/10.1074/jbc.M110.147413. PubMed.

143 Yang L, Gao Z, Hu L, Wu G, Yang X, Zhang L, et al. Glycoarylphosphatidylinositol anchor modification machinery deficiency is responsible for the formation of pro-prion protein (PrP) in BxPC-3 cells and increases cancer cell motility. J Biol Chem. 2016;291(13):6785. doi: http://dx.doi.org/10.1074/jbc.A115.705830. PubMed.

144 Lu W, Kang Y. Epithelial-Mesenchymal Plasticity in Cancer Progression and Metastasis. Dev Cell. 2019;49(3):361–74. doi: http://dx.doi.org/10.1016/j.devcel.2019.04.010. PubMed.

145 Shibue T, Weijsing RA. EMT, CSCs, and drug resistance: the mechanistic link and clinical implications. Nat Rev Clin Oncol. 2017;14(10):611–29. doi: http://dx.doi.org/10.1038/nrclinonc.2017.44. PubMed.

146 Martin-Lannerée S, Hirsch TZ, Hernandez-Rapp J, Halliez S, Vilotte JL, Launay JM, et al. PrP(C) from stem cells to cancer. Front Cell Dev Biol. 2014;2:55. PubMed.

147 Raymond GJ, Zhao HT, Race B, Raymond LD, Williams K, Swazy EE, et al. Anti-sense oligonucleotides extend survival of prion-infected mice. JCI Insight. 2019;4(10):. doi: http://dx.doi.org/10.1172/jci.insight.131175. PubMed.

148 Barberi G, Palumbo S, Gabrusiewicz K, Azzalin A, Marchesi N, Spedicato A, et al. Silencing of cellular prion protein (PrPc) expression by DNA-anti-sense oligonucleotides induces autophagy-dependent cell death in glioma cells. Autophagy. 2011;7(8):840–53. doi: http://dx.doi.org/10.4161/auto.7.8.15615. PubMed.

149 Spagnoli G, Rigoli M, Orioli S, Sevillano AM, Faccioli P, Wille H, et al. Full acrosomal model of prion structure and conversion. PLoS Pathog. 2019;15(7):. doi: http://dx.doi.org/10.1371/journal.ppat.1007864. PubMed.
Author/s:
Manni, G; Lewis, V; Senesi, M; Spagnolli, G; Fallarino, F; Collins, SJ; Mouillet-Richard, S; Biasini, E

Title:
The cellular prion protein beyond prion diseases.

Date:
2020-04-20

Citation:
Manni, G., Lewis, V., Senesi, M., Spagnolli, G., Fallarino, F., Collins, S. J., Mouillet-Richard, S. & Biasini, E. (2020). The cellular prion protein beyond prion diseases.. Swiss Med Wkly, 150 (17), pp.w20222-. https://doi.org/10.4414/smw.2020.20222.

Persistent Link:
http://hdl.handle.net/11343/274173

File Description:
Published version

License:
CC BY-NC-ND