Prion protein scrapie and the normal cellular prion protein

Caroline J. Atkinson\textsuperscript{a}, Kai Zhang\textsuperscript{a}, Alan L. Munn\textsuperscript{b}, Adrian Wiegmans\textsuperscript{c},
and Ming Q. Wei\textsuperscript{a}

\textsuperscript{a}Division of Molecular and Gene Therapies, Menzies Health Institute, Griffith University, Gold Coast, QLD, Australia;
\textsuperscript{b}Laboratory of Yeast Cell Biology, Molecular Basis of Disease Program, Menzies Health Institute Queensland and School of Medical Science, Griffith University, Gold Coast, QLD, Australia;
\textsuperscript{c}Tumour Microenvironment Laboratory, QIMR Berghofer Medical Research Institute, Herston, Australia

\textbf{ABSTRACT.} Prions are infectious proteins and over the past few decades, some prions have become renowned for their causative role in several neurodegenerative diseases in animals and humans. Since their discovery, the mechanisms and mode of transmission and molecular structure of prions have begun to be established. There is, however, still much to be elucidated about prion diseases, including the development of potential therapeutic strategies for treatment. The significance of prion disease is discussed here, including the categories of human and animal prion diseases, disease transmission, disease progression and the development of symptoms and potential future strategies for treatment. Furthermore, the structure and function of the normal cellular prion protein (PrP\textsuperscript{C}) and its importance in not only in prion disease development, but also in diseases such as cancer and Alzheimer’s disease will also be discussed.

\textbf{KEYWORDS.} bovine spongiform encephalopathy, infectious protein, Creutzfeldt-Jakob disease, PRNP, Alzheimer’s disease, prion treatment
INTRODUCTION

Some prion proteins have become well known for their causative role in a range of neurodegenerative diseases in humans and other mammals. Human prion diseases include Creutzfeldt-Jakob Disease (CJD), Gerstmann-Sträussler-Scheinker disease (GSS), Familial Fatal Insomnia (FFI), kuru and variant CJD (vCJD). Animal prion diseases include Scrapie in sheep, goats and mouflons (subspecies of wild sheep), Transmissible Mink Encephalopathy, Chronic Wasting Disease in deer (cervids), Bovine Spongiform Encephalopathy (BSE) in cattle, Exotic Ungulate Encephalopathy in nyala and kudu (sub-species of antelope). Feline Spongiform Encephalopathy in cats, Non-human Primate Transmissible Encephalopathy in lemurs. Over the past decade, significant research has been conducted to establish not only the types of prion diseases and their infection mechanisms, but to find an effective therapeutic strategy for treatment.

PRION DISEASE

Prion diseases have a number of common histopathological characteristics and neurological symptoms. These include spongiform degeneration of the central nervous system (CNS), formation of amyloid plaques, reactive gliosis (enlarged glial cells appearing after CNS injury) and neuronal loss. Other atypical properties characteristic of prion diseases are long incubation periods (which can extend from several months to several years), lack of inflammation and lack of disease-specific immune response.

While at first these neuronal degeneration diseases were thought to be caused by “slow” viruses due to their long incubation periods, neither viral particles nor nucleic acids could be detected to support the hypothesis that these are viral diseases. The viral hypothesis also failed to account for the finding that 95% of human neuronal degeneration disease cases are not linked to infection and lacked the typical histopathological features of viral encephalitis. Hence, the viral disease hypothesis failed to adequately account for the findings that emerged from studies of these diseases. It was also discovered that between 10 and 15% of these neuronal degeneration diseases are dominantly inherited, including all cases of GSS and FFI and 10% of cases of CJD. The latter are referred to as familial CJD (fCJD). In summary, the data showed that these neuronal degenerative diseases can be both infectious and inherited.

During the attempts to uncover the molecular basis of prion diseases over the past few decades, it was uncovered that the causative agent of scrapie, is a 27-30kDa protease-resistant protein designated as PrP 27-30. PrP 27-30 was found to be encoded by a single mammalian gene located on human chromosome 20. This gene was designated PRNP. Other animals have a homolog of the human PRNP gene and this gene was named Prnp. Furthermore, it was discovered that PrP27-30 was derived from a 30-35kDa protein in scrapie-infected animals, designated prion protein scrapie (PrPSc). PrPSc was discovered to be a derivative of the normal protease-sensitive form of PrP that was designated cell-surface glycoprotein (PrPC). Upon further investigation, it was found that all dominantly inherited forms of prion diseases are linked to mutations of or insertions in the PRNP gene.

Development of Prion Disease

Neurodegenerative prion diseases such as CJD, Kuru and BSE, result from the post-translational conversion of normal, glycosyl-phosphatidylinositol (GPI)-anchored PrPC to a misfolded aggregated and pathogenic form, PrPSc. This conversion followed by an accumulation of PrPSc within the central nervous system resulting in disease (Fig. 1).

As shown in Figure 1, the newly formed PrPSc acts as a template to facilitate conversion of PrPC to PrPSc, causing the accumulation of PrPSc. This process takes place regardless of the origin of the PrPSc, i.e. whether it is from an external source or a produced internally due to mutations in the PRNP gene (as in the case in fCJD and FFI) or due to a spontaneous
conversion of wild-type PrP$^C$ to PrP$^Sc$, which is referred to as ‘de novo generation/synthesis’.14

PrP$^Sc$ is characterized by its resistance to protease digestion, insolubility and its high content of β-sheet structure$^{15,16}$ (43% β-sheets compared to 30% α-helical). In contrast, PrP$^C$ is an soluble protein high in α-helices (42%), low in β-sheet (3%) and highly susceptible to protease digestion.$^{13}$ PrP$^C$ contains 2 different domains that play different roles in the conversion of PrP$^C$ to PrP$^Sc$. The first is a stable and ordered ‘core’ domain which contains a GPI lipid anchor that tethers PrP$^C$ to the plasma membrane, 3 α-helices (helices A, B and C) (Fig. 2), 2 asparagines-linked oligosaccharides and a protein binding site capable of lowering the energy barrier for conversion of PrP$^C$ to PrP$^Sc$ when PrP$^C$ binds to protein X (a species specific cofactor necessary for conversion of PrP$^C$ to PrP$^Sc$).$^{17,18}$ The second domain is a ‘variable’ or disordered domain which interacts with PrP$^Sc$ and changes PrP$^C$ conformation from the unstructured form to the β-sheets of PrP$^Sc$ (Fig. 2).$^{16}$ During conversion of PrP$^C$ to PrP$^Sc$, helix A of the core domain of PrP$^C$ (Fig. 2) also gets converted into β-sheets.$^7$

**Types of Prion Disease**

Prion diseases in humans and animals have thus far been classified into 3 broad categories, based on the properties of the corresponding pathogenic PrP proteins that accumulates in the brain and on their neuroanatomical features of the prion-infected brain$^7$ as summarized in Table 1.

The oral route of infection is the major mode of transmission for most cases of acquired prion diseases in humans. The spread of the diseases via this route, both naturally and experimentally, has been described in many species. Kuru, for example, was shown to be spread among the Fore people who populate the eastern highlands of Papua New Guinea through ingestion of infected brain tissue during cannibalistic rituals which resulted in a particularly high incidence of the disease$^{23-25}$
The sCJD accounts for more than 90% of all cases of sporadic prion disease. However, not all CJD is sporadic. Beginning in the 1980s when a considerable number of cattle were killed by BSE concerns about the spread of BSE to humans grew dramatically in the United Kingdom. The concern was that BSE could spread to humans through ingestion of infected beef, a fear which was realized in 1995. A new form of CJD was first reported by the UK National CJD Research and Surveillance Unit in 1996, and is now known as variant CJD (vCJD). It is believed that vCJD possesses distinct clinical and neuropathological characteristics from sporadic CJD (sCJD) and other forms of prion disease in human. The main distinguishing neuropathological feature of vCJD is an extensive deposition of PrPSc amyloid in the brain in the form of large ‘florid’ plaques. Other phenotypes include a younger average age of onset, and gliosis of the thalamus. Epidemiological studies supported the possibility that the outbreak of BSE in cattle in the UK in the same period may have been

TABLE 1. Summary of the 3 broad categories of prion diseases and the defining characteristics of each

| Category | Prion Disease | Defining characteristics | References |
|----------|---------------|--------------------------|------------|
| 1        | Scrapie, sporadic, familial and iatrogenic CJD (sCJD, fCJD, iCJD), BSE, kuru and sporadic and familial fatal insomnia (sFI and fFI) | Vacular (spongiform) degeneration of gray matter, accumulation of protease resistant PrPSc in gray matter, little or no PrP amyloid plaque formation. | 7 |
| 2        | Dominantly inherited syndromes (GSS) | Deposition of numerous PrP immunopositive amyloid (abnormal protein) plaques in multiple cortical and subcortical brain regions, PRNP mutation. | 7,19 |
| 3        | Variant CJD (vCJD) | PrPSc amyloid deposition, vacuolation of gray matter, accumulation of protease resistant PrPSc in neuropil (space between neuronal and glial cell bodies comprised of dendrites, axons, synapses microvasculature and glial cell processes). | 7,19-22 |
responsible for the emergence of vCJD. Subsequently, experimental transmission studies of vCJD and BSE in mice proved that the vCJD agent, unlike the agent responsible for sCJD, had biological properties closely similar to those of the BSE agent.\textsuperscript{20,30} Therefore, vCJD has been confirmed as a novel prion disease and the only human prion disease acquired from another species. Subsequent studies suggested that the pathogen could be present in blood during the incubation period for vCJD,\textsuperscript{31,32} and that exposure to such blood could result in the infection of humans or other animals. Therefore, the UK National CJD Surveillance Unit reported that vCJD is caused by exposure to BSE and that the primary source of exposure is the consumption of infected meat products.\textsuperscript{29}

Unlike vCJD, Iatrogenic CJD is an entirely person to person transmitted disease, identified to be transmitted through a number of mechanisms including contaminated surgical instruments,\textsuperscript{33} and dura mater grafts,\textsuperscript{34} blood transfusions\textsuperscript{35} and injection of products from cadaveric pituitary glands.\textsuperscript{36,37} The first case of iCJD was described in 1974 where a corneal graft recipient died after acquiring a dementia-like likeness.\textsuperscript{38} With improved screening and sterilisation techniques, rates of iCJD continue to decrease with new cases that occur often the result of longer incubation periods following infection acquired in the 1980s.\textsuperscript{39,40}

Whereas the causes of prion diseases that are genetically inherited or acquired by infection have been extensively studied and now quite well known, the cause of sporadic prion diseases is still a topic of speculation.\textsuperscript{41} Among the many mechanisms that have been proposed to provoke sporadic prion disease, the mechanism that is supported by the most compelling evidence is a mechanism in which malfunction of the so called quality control complex in cells is responsible for initiation of the disease.\textsuperscript{42} The cellular quality control complex acts like a set of enzymes which assist newly synthesized polypeptides to “grow” to their proper conformation and also play a role in disposal of those polypeptides that fail to adopt the native structure. Therefore, a lowered efficiency of the quality control complex, perhaps due to aging or if the quality control complex becomes overwhelmed by excessive protein production, may result in errors in protein folding occurring and the production of misfolded proteins.

One of the inherited prion diseases is Gerstmann–Sträussler–Scheinker disease (GSS). GSS is caused by a pathological mutation in the prion protein gene (PRNP) located on chromosome 20. It is a very rare disease with autosomal dominant inheritance. The age of onset of GSS is relatively early but the disease progresses slowly with an average illness duration of 49–57 months (until death).\textsuperscript{43,44} The typical GSS syndrome includes prominent ataxia, gait disturbances, cognitive decline and spasticity in the lower extremities.\textsuperscript{35,46} Rarely the syndrome may also include painful dysesthesias and visual disturbances, dystonia and myoclonus and dementia.\textsuperscript{45,47,48} A GSS case attributable to an A133V mutation in PRNP resulted in an uncommon phenotype similar to that of progressive supranuclear palsy.\textsuperscript{49} Several other pathological variations that cause GSS have been described. The most common mutation in PRNP is P102L, which is found in more than 80% of cases.\textsuperscript{50} The P102L mutation was found in the original GSS pedigree.\textsuperscript{51} Other mutations in PRNP known to cause GSS include P105L, P105S, A117V, G131V, Y145*, H187R, D202N, Q212P, Q217R, M232T, and base-pairs insertions at positions 96, 192, or 216.\textsuperscript{52}

Recently, several GSS cases with novel PRNP mutations were reported. A 61-year-old British-born woman with no history of neurodegenerative disorder among her first-degree relatives in Australia presented with a rapidly progressive dementia. Sequencing of the PRNP gene demonstrated a V176G mutation. Subsequent Western blot analysis resulted in the detection of an 8 kDa atypical protease-resistant PrP band.\textsuperscript{53} Sequencing of the PRNP gene of another GSS patient (this one in North America) revealed a 24-nucleotide insertion that when translated would result in a protein product with an 8-amino acid insertion.\textsuperscript{54} Independent neuropathological studies of 2 GSS pedigrees with the P102L mutation obtained divergent findings.\textsuperscript{55,56} The authors note that the variable clinical presentation of GSS patients (even those with the same PRNP...
mutation) makes diagnosis of GSS challenging and in some families the presence of GSS may be missed. Routine clinical and laboratory investigations, sequence analysis of the PRNP gene and post-mortem examination are recommended in all cases with a family history of any type of neuropsychiatric syndrome.

**Treatment of Prion Disease**

There are currently no treatments that have proven effective for curing prion diseases in humans or animals. However, monoclonal antibodies that recognize PrP<sup>Sc</sup> and PrP<sup>C</sup> have been shown to inhibit prion replication and delay prion disease development in animals models.\(^57\) These antibodies block PrP<sup>Sc</sup> replication by accelerating the degradation of PrP<sup>C</sup> (i.e., through reduction of the half life of the PrP<sup>C</sup> protein).\(^58\)

Another strategy has been the use of low molecular weight compounds. Compounds that have been undergoing clinical investigation as a possible therapy for prion disease include heterocyclic compounds, e.g. various tricyclic derivatives of acridine and phenothiazine, particularly quinacrine and chlorpromazine.\(^59,60\) Treatments such as this have been shown to be effective in inhibiting the formation of nascent PrP<sup>Sc</sup> from PrP<sup>C</sup> in ScN2a (human neuroblastoma) cells.\(^59,61\) These chemicals have been in clinical use for many years, quinacrine as an antimalarial drug and chlorpromazine as an antipsychotic drug, and both are capable of crossing the blood-brain barrier. Treatments with these chemicals are therefore considered to be attractive options for use essentially “as is” in treatment of prion infections.\(^59,62\)

Quinacrine has been shown the ability to inhibit the formation of PrP<sup>Sc</sup> in ScN2a cells with an IC\(_{50}\) of 0.3–0.4 \(\mu\)M.\(^59,61\)

A study by Barrett et al.\(^62\) re-evaluated the potential of quinacrine and chlorpromazine as treatments for prion diseases. The efficacies of these drugs were assessed in vitro using 2 cell line models (ScN2a and ScGT1) and in vivo using a mouse model. While the results obtained from the previous studies using the ScN2a cell line were replicated in this study for the ScN2a cell line, this study obtained different results from previous studies for the ScGT1 cell line. In contrast to the findings from the previous studies using ScGT1 cells, this study found that only higher doses of chlorpromazine and quinacrine (10 times the concentration previously described, 4 \(\mu\)M) decreased PrP<sup>Sc</sup> accumulation in ScGT1 cells in a single treatment. Lower doses of quinacrine (0.4 \(\mu\)M) cured ScGT1 cells only over longer treatment times (i.e. daily treatment for 3 weeks) and the effect was not permanent as PrP<sup>Sc</sup> infection was re-established after approximately 3 months. Furthermore, quinacrine and chlorpromazine failed to inhibit PrP<sup>Sc</sup> accumulation in vivo (either individually or even in combination). It was also noted that quinacrine treatment did not affect the proteinase K-resistance or accumulation of PrP<sup>Sc</sup> in the spleens of mice inoculated with scrapie. Thus overall the studies show that quinacrine and chlorpromazine, individually or in combination, do not have therapeutic anti-prion effects in animal models and highlights the need for new and more effective therapeutics.

Doxycycline has been used as a compassionate treatment for CJD patients and was observed to increase mean survival times by 4-7 months in comparison to historical controls. Furthermore, a patient with variably protease-sensitive prionopathy was treated from an early stage and for 4 years in total with doxycycline and not only lived one year longer than the longest surviving patient with that subgroup of prion disease, but also had less severe and widespread lesions.\(^63\) However, while indeed promising these beneficial effects were not confirmed in randomized, double-blind trials.\(^64\) In experimental rodent models of prion disease, treatment with doxycycline at early stages (i.e., pre-clinical onset) showed good efficacy, while there was little or no apparent effect once clinical signs had emerged.\(^65\) This suggests that treatment with doxycycline may be most useful as a preventive measure, for example for those patients who are carriers of the PRNP mutation that causes Familial Fatal Insomnia,\(^66\) and this trial is currently underway.\(^67\)

A recent study has shown that treatment of prion disease in humans with non-human prion
proteins may be a viable treatment option. This approach is based on the knowledge that conversion of PrP\textsuperscript{C} to PrP\textsuperscript{Sc} has a strong dependence on protein sequence homology between the prion inoculum and host PrP\textsuperscript{C}.\textsuperscript{68-70} Skinner et al.\textsuperscript{71} showed that animals treated with a heterologous prion protein (bacterially expressed and purified recombinant hamster prion protein), demonstrated reduced prion-disease-associated pathology, decreased accumulation of protease-resistant disease associated prion protein and delayed onset of clinical symptoms (including motor deficits), as well as significantly increased mean survival times in comparison to mock-treated control animals.

**THE NORMAL CELLULAR PRION PROTEIN**

PrP\textsuperscript{C}, as mentioned previously, is the normal cellular form of the causative agent of PrP\textsuperscript{Sc} and is required for the development of all the above-mentioned prion diseases. Expression of PrP\textsuperscript{C} begins in embryogenesis, and expression reaches its highest level in adulthood. In adults, PrP\textsuperscript{C} is highly expressed in the neurons of the nervous system,\textsuperscript{72} and lower, or no expression is observed in other peripheral organs.\textsuperscript{73} While the 3-dimensional structure and a number of putative roles of PrP\textsuperscript{C} have been reported the exact biochemical function of PrP\textsuperscript{C} is yet to be elucidated.

**Processing, 3D Structure and Putative Physiological Role of PrP\textsuperscript{C}**

**3D Structure of PrP\textsuperscript{C}**

PrP\textsuperscript{C} is generally located on the cell membrane and associates with cholesterol-rich microdomains (rafts) in cultured non-neuronal and neuronal cells.\textsuperscript{74} The immature PrP\textsuperscript{C} protein is approximately 253 amino acid residues long and 32-35kDa in mass and comprises of an unstructured N-terminal region and a structured C-terminal domain. The C-terminal domains consists of 3 \(\alpha\)-helices, a \(\beta\)-sheet comprising 2 antiparallel \(\beta\)-stands\textsuperscript{75} and a signal sequence for attachment of the GPI anchor.\textsuperscript{76} The unstructured N-terminal domain contains an octarepeat and a hydrophobic region.

**Processing of PrP\textsuperscript{C}**

In order to form a mature protein PrP\textsuperscript{C} undergoes a number of posttranslational modifications and these are initiated by the removal of the N-terminal and C-terminal signal peptides which is coincident with import of the nascent chain into the endoplasmic reticulum and attachment of the GPI anchor. Two N-linked glycans are also attached and this is followed by a disulphide bond between Cys178 and Cys213.\textsuperscript{77,78} This disulphide bond is important as it connects the C-terminal \(\alpha\)-helices, and serves to stabilize the fold of the PrP\textsuperscript{C} protein.\textsuperscript{79} PrP\textsuperscript{C} (which is 210 amino acid residues in length)\textsuperscript{77} is then targeted to the outer leaflet of the plasma membrane by the GPI-anchor.\textsuperscript{77,78} PrP\textsuperscript{C} can also undergo 2 endopeptidase cleavage events.\textsuperscript{80} The normal constitutive cleavage, known as \(\alpha\)-cleavage\textsuperscript{81} (Fig. 3B), occurs in the brain and in cultured cells between residues 110 and 111. This cleavage is stimulated by agonists of the protein kinase C pathway\textsuperscript{82} and results in the formation of a 9kDa soluble N-terminal fragment and a 17kDa C-terminal fragment that remains attached to the cell membrane via the GPI anchor.\textsuperscript{83-85} The second cleavage, known as \(\beta\)-cleavage\textsuperscript{81} (Fig. 3C), is mediated by reactive oxygen species (ROS)\textsuperscript{81,86} and leads to the formation of a 19kDa GPI-anchored C-terminal fragment and a 7kDa N-terminal fragment.\textsuperscript{84,85,87}

PrP\textsuperscript{C} can then undergo a third cleavage (known as ectodomain shedding) in which PrP\textsuperscript{C} is cleaved at a site close to the GPI anchor thus releasing the nearly full-length PrP\textsuperscript{C} protein from the plasma membrane into the extracellular medium. This proteolytic cleavage has been shown to be performed by the sheddase ADAM10.\textsuperscript{88-90} Release of PrP\textsuperscript{C} from the cell surface has not only been demonstrated in cell culture, but also in neuronal and lymphoid cells in vivo.\textsuperscript{88,91-93}
Copper Regulation

PrP^C is a metal ion-binding protein. It binds copper and zinc with high affinity and manganese and nickel cations with a lower affinity. Copper binding involves the histidine residues located within the octarepeat region of the N-terminal domain, although recent studies reveal additional copper-binding sites. Since the N-terminal domain is also involved in the binding of PrP^C to a number of protein ligands, it has been hypothesized that copper binding may play a structural role and influence the binding of PrP^C to these other proteins.

In support of a possible physiological role for PrP^C in copper homeostasis, it has been shown that PrP^C-deficient (PRNP null) mice exhibit a 50% lower copper concentration in synaptosomal fractions in comparison to wild type mice. This suggests that PrP^C may be involved in the regulation of copper concentrations in the synaptic region of the neuron, e.g., by playing a role in the uptake of copper into presynaptic cells. Furthermore, PrP^C endocytosis has been shown to be stimulated when copper is added to cultured neuroblasto
toma cells, suggesting that PrP^C internalisation may be involved in the transport of copper from extracellular to intracellular compartments. It may also indicate that PrP^C functions as a copper buffer, binding the copper and transferring it to another membrane transporter.

Qin and colleagues reported that in murine neuro-2a and human HeLa cells, endogenous PrP^C rapidly reacts with Cu^{2+}. Cu^{2+} elevates PrP^C expression through transcriptional up-regulation mediated by the ataxia-telangiectasia mutated (ATM) transcription factor. Elevation of PrP^C expression protects the cell against copper-induced oxidative stress (and therefore prevents cell death) by playing a role in the modulation of intracellular copper concentrations.

Recently, PrP^C has further been shown to function as a modulator of heavy metal concentrations, protecting cells against heavy metal build-up and thus oxidative stress. It was shown...
in cells with full-length PrP<sup>C</sup> were more resistant to chronic overload of heavy metals (copper, zinc, nickel and manganese) than their PrP-knock out counterparts.  

**Signal Transduction**

PrP<sup>C</sup> has been hypothesized to modulate various signaling pathway components involved in proliferation, cell adhesion, transmembrane signaling, differentiation, and trafficking. For example, PrP<sup>C</sup> has been shown to have a functional link to phosphatidylinositol 3 kinase (PI-3), a protein kinase involved in cell survival, with *in vitro* (cell line) and *in vivo* (mouse) studies showing cells that express PrP<sup>C</sup> have higher PI-3 levels than those without PrP<sup>C</sup>. PrP<sup>C</sup> has further been shown to transduce neuroprotective signals through the cyclic AMP-dependent protein kinase/protein kinase A (PKA) pathway as well as Fyn and many others.

**Immune System**

PrP<sup>C</sup> has recently been reported to play a role in the development, activation and proliferation of T lymphocytes. While PrP<sup>C</sup> is widely expressed in the immune system including in human T and B lymphocytes, natural killer cells, platelets, monocytes, and dendritic cells, it has been found to be up-regulated during T-lymphocyte activation and at even more upregulated during natural killer cell differentiation. Follicular dendritic cells show high expression of PrP<sup>C</sup>, however, mice with follicular dendritic cell specific PrP<sup>C</sup> knock down, showed no alteration in on maturation or function of follicular dendritic cells, indicating the high expression or PrP<sup>C</sup> is non-essential. In contrast, PrP<sup>C</sup> expression has been shown to be important for macrophage function, modulating phagocytosis *in vitro* and *in vivo*.

PrP<sup>C</sup> has been found to physically interact with a signal transduction protein with an important role in T lymphocyte activation and proliferation: zeta-chain-associated protein (ZAP)-70. In addition, the expression of interleukin-2 is increased when PrP<sup>C</sup> is expressed. These observations suggest that PrP<sup>C</sup> is involved in the development, activation and proliferation of T-lymphocytes. Furthermore, a recent study showed a soluble recombinant form of PrP<sup>C</sup> activates human natural killer cells via the ERK and JNK signaling pathways, facilitating IL-15 induced proliferation of natural killer cells, as well as inducing phosphorylation of ERK1/2 and JNK.

**Protection from Programmed Cell Death**

When PRNP was knocked out in mice, there was no alteration of life span or observed change in the phenotype of mice, indicating that PrP<sup>C</sup> has a non-critical function or its function is taken over by another protein in its absence. However, further research into the function of PrP<sup>C</sup> in the CNS demonstrated that its absence in hippocampal neurons resulted in apoptotic (programmed) cell death. PrP<sup>C</sup> also has a structural similarity to the BH2 domain of B-cell lymphoma (Bcl)-2 family members, resulting in the suggestion that PrP<sup>C</sup> may also function as a member of this family of proteins. It was demonstrated that *in vitro*, PrP<sup>C</sup> protects human neurons against Bcl-2-associated X protein (Bax)-mediated cell death, a pro-apoptotic protein that accelerates cell death by initiating the release of apoptotic factors by mitochondria. When Bcl-2 and Bax are co-expressed, hyperactivation of Bax-induced apoptosis is prevented. Similarly, co-expression of PrP<sup>C</sup> with Bcl-2 also prevented Bax-induced cell death, implying that PrP<sup>C</sup> may play a role in protection of neurons against Bax-induced cell death.

**Role of PrP<sup>C</sup> in Central Nervous System Functions**

Electrophysiological *in vivo* studies on PrP-null mice have found that PrP<sup>C</sup> influences a number of processes within the CNS. These studies demonstrated a number of functional abnormalities in the hippocampus. First there was reduced gamma-aminobutyric acid type A/GABA<sub>A</sub> receptor-mediated synaptic
transmission (GABAa is a ligand-gated ion channel and voltage-dependent calcium channel that play a role in synaptic transmission and regulation of neuronal excitability). Another defect observed in PrPc neurons was attenuation of long-term potentiation. Long-term potentiation is the long-lasting signal transmission between neurons involved in memory. Furthermore, the PrPc neurons exhibited slow after hyperpolarization (i.e. prolonged phase of an action potential in which the membrane potential of a neuron falls below resting potential). Other defects in PrPc-null neurons included: disruption of calcium currents, activation of potassium currents, reduction in the amplitude of inhibitory postsynaptic potentials and abnormal reorganization of the mossy fiber circuitry in the hippocampus.

Impairment in hippocampus-dependent spatial learning and altered excitatory and inhibitory neurotransmission in PrP-null mice further support the proposed role of PrP in synaptic function. Studies have also found changes in motility, anxiety and equilibrium in adult mice that were attributable to reduced levels of PrPc. In addition, PrPc has been shown to bind to the neural cell adhesion molecule (NCAM) which is a signaling receptor in the nervous system that takes part in a number of developmental processes including cell migration, synaptic plasticity and neurite outgrowth. In summary, these various studies suggests that PrPc may play a role in CNS development through effect on directed cell migration of neural progenitor cells and the spatial coordination of the outgrowth of neurites as well as playing a role in neuronal survival.

**Potential Role of PrPc in Cancer Development, Progression And Multi-Drug Resistance**

Evidence supporting a role of prions and/or prion-like proteins in cancer is becoming increasingly significant. PrPc has been shown to be highly expressed in a number of cancers including pancreatic, gastric, breast, prostate and colorectal and multi-drug resistant forms of breast and gastric. Consistant with this, over-expression of PrPc has also been reported in a number of human gastric cancer cell lines including SCG7901 and AGS. PrPc was also found to be expressed in gastric carcinoma tissues using immunohistochemical staining. Du et al. discovered that PrPc is expressed more strongly in gastric adenocarcinoma tissues than in adjacent non-tumorous tissues and is weakly, or not expressed, in normal gastric mucosa.

PRNP was found to be over-expressed in pancreatic ductal adenocarcinoma (PDAC) in a microarray study by Han et al. Another study investigated 7 human PDAC cell lines to determine whether PrPc is overexpressed. While PrPc is over-expressed in the PDAC cell lines, it exists in the form of a pro-protein (Pro-PrP) and is neither glycosylated nor GP-anchored.

RT-PCR analysis conducted on surgically removed colorectal cancer specimens revealed that PRNP expression is up-regulated in colorectal carcinoma when compared to normal colorectal tissue. This suggests a role for PrPc in the development of colorectal cancer. Examination of PrPc expression in colorectal cancer was conducted using formalin-fixed paraffin-embedded colonic neoplastic tissue sample from 110 patients. This study also found that PrPc protein expression increased in cancerous colorectal tissues in comparison to normal colorectal tissues and, moreover, that the differential expression in these tissues was even greater than that observed for PRNP mRNA levels in the previous study.

Study of differential gene expression profiles revealed that PRNP gene is upregulated in the adriamycin-resistant gastric carcinoma cell line (SGC7901/ADR) when compared to its parental cell line SGC7901. This indicates that PrPc may have a role in the development of multi-drug resistance (MDR) phenotypes in gastric carcinomas and has led to a focus on PrPc expression levels in gastric cancer and the
mechanisms of PrP C action within MDR gastric carcinoma relevant to its acquisition of MDR phenotypes.73

PrP C has been shown to promote the metastasis of colorectal cancer by mediating epithelial-mesenchymal transition (EMT). It was shown that PrP C expression is associated with the invasive front of colorectal cancer where cells display the characteristics of EMT and that PrP C expression facilitates tumor invasion. Furthermore, functional assays showed that ectopic PrP C expression promotes metastatic potential while knock-down reduces motility of cells. Additionally, knock down of PrP C in implanted colorectal cancer cells in orthotopic xenograft mouse model abolished the number of distant metastases. It was shown that PrP C accelerates tumor metastasis by upregulation of SATB1 expression via the Fyn-SP1 pathway.141 SATB1, a matrix attachment region binding protein important for tissue-specific gene expression, has been shown to alter the gene expression profile of cancer cells to induce an aggressive phenotype and promote metastasis. Depletion of SATB1 reduces cancer progression and results in a metastatic cells undergoing transition to a normal phenotype.142 The molecular signaling events downstream of PrP C were abolished when the Fyn tyrosine kinase was inhibited. This indicates a requirement for Fyn kinase signaling for PrP C-mediated SATB1 expression. Furthermore, SP1 inhibition also reduced SATB1 expression and the metastatic potential of colorectal cancer cells. Overall, this study showed for the first time a link between PrP C expression levels and colorectal cancer metastasis and furthermore showed that the signaling is through a PrP C-Fyn-SP1-SATB1 axis. This signaling pathway may represent a potential target for the future development of anti-metastasis drugs.141

Once it had been confirmed that PrP C is overexpressed in gastric cancer tissues relative to adjacent non-tumor tissues and normal gastric mucosa,73 studies were performed to assess whether PrP C expression level influences the invasive and metastatic properties of gastric cancer. While PrP C was found to be more highly expressed in metastatic cancer than non-metastatic cancer, there was no significant correlation between PrP C expression levels at the primary site and at the metastatic site of the same metastatic gastric cancer. This suggests that an increase in PrP C expression is an early determinant of metastasis and may be useful as a prognostic factor. PrP C expression was also shown to promote adhesive, invasive and metastatic properties of gastric cancer cells in vivo. The N-terminal region of PrP C exhibits an invasion-promoting effect through the activation of the mitogen-activated protein kinase (MAPK)/extracellular-signal-regulated kinase (ERK) pathway or the MEK/ERK pathway [11]. The MEK/ERK pathway controls cellular processes such as proliferation, apoptosis, survival and differentiation.143 In part, MEK/ERK signaling controls these processes by the transactivation of expression of MMP11 (matrix metalloproteinase 11) [11]. MMP11 in turn is promotes matrix degradation, inflammation and tissue remodeling.144

Potential Role of PrP C in Alzheimer’s

Alzheimer’s disease accounts for 60% to 70% of all cases of dementia.145 There are 2 core pathological hallmarks of Alzheimer’s disease: amyloid plaques and neurofibrillary tangles. The cause of the disease is complex, but the amyloid hypothesis proposes that extracellular amyloid plaques comprising the protein amyloid β (Aβ) is the fundamental cause of the disease. The deposition of Aβ in the brain could trigger neuronal dysfunction and cause neuronal cell death.146 Several studies have shown a physical interaction between Aβ oligomers and PrP C. These studies have provided evidence that the Aβ-PrP C interaction may play an important role in the Aβ toxicity at the synapse by perforating membranes, increasing intracellular calcium ion concentrations and release of synaptic vesicles.147 Recently, it has been shown that sodium dextran sulphate inhibits the binding of Aβ to PrP C and furthermore that simultaneous treatment with sodium dextran sulphate protects long-term potentiation in mouse hippocampal slices from the toxic effects of Aβ oligomers.148

Like Alzheimer’s disease,149,150 human prion diseases are associated with a number of
psychiatric and behavioral symptoms such as depression and anxiety. It has been speculated that the monoaminergic system plays a role in the development of some of these symptoms. It has been shown that PrP<sup>C</sup>-null mice display depressive-like behavior, and recently, PrP<sup>C</sup> has been shown to regulate the functions of the monoaminergic systems. The authors suggest that the loss of PrP<sup>C</sup> function in neurodegenerative diseases, attributable to the accumulation of PrP<sup>Sc</sup> in prion diseases and binding of Aβ oligomer to PrP<sup>C</sup> in Alzheimer’s disease interferes with the monoaminergic signaling thus resulting in the neuropsychotic manifestations of these diseases. In support of this hypothesis, the behavioral phenotypes of PrP<sup>C</sup>-null mice have similarities to the behavioral effects observed following injection of wild type Aβ peptide oligomers. Overall, recent studies indicate that PrP<sup>C</sup> may be a potential target for the future development of drugs to treat depression and depression-related disorders.

**CONCLUSION**

Investigations into prion disease and suitable treatments continue to advance. However, a cure for these diseases still appears to be a distant possibility. Additionally, although decades of research have uncovered a vast range of information about PrP<sup>C</sup>, there is still much that remains to uncover, particularly in relation to the exact molecular function of PrP<sup>C</sup>. While PrP<sup>C</sup> does not appear to be essential, with some studies showing PRNP knock out mice displaying no apparent deficiencies, and others showing minor behavioral changes, PrP<sup>C</sup> does appear to have a range of important functions. Even more interestingly, the role of PrPC in the development and progression of cancer as well as other diseases such as Alzheimer’s disease, is receiving increasing research attention. While the exact role of PrP<sup>C</sup> in these other diseases remains undetermined, existing research has already shown PrP<sup>C</sup> to be a potential target for the future development of drug treatments for these other diseases.

**ABBREVIATIONS**

- BSE: Bovine Spongiform Encephalopathy
- CJD: Creutzfeldt-Jakob Disease
- Fcjd: familial CJD
- FFI: Familial Fatal Insomnia
- GSS: Gerstmann-Sträussler-Scheinker disease
- iCJD: iatrogenic CJD
- PrP: Prion Protein
- PrP<sup>C</sup>: Cellular Prion Protein
- PrP<sup>Sc</sup>: Prion protein scrapie
- sFI: sporadic fatal insomnia
- vCJD: variant CJD

**DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST**

Authors confirm there is no conflict of interest.

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**REFERENCES**

[1] Collinge J. Prion diseases of humans and animals: their causes and molecular basis. Annu Rev Neurosci 2001; 24:519-50; PMID:11283320; http://dx.doi.org/10.1146/annurev.neuro.24.1.519

[2] Prusiner SB. Prions. Proc Natl Acad Sci 1998; 95:13363-13383; PMID:9811807; http://dx.doi.org/10.1073/pnas.95.23.13363

[3] Jeffrey M, Gonzalez L. Classical sheep transmissible spongiform encephalopathies: pathogenesis, pathological phenotypes and clinical disease. Neuropathol Appl Neurobiol 2007; 33(4):373-94; PMID:17617870; http://dx.doi.org/10.1111/j.1365-2990.2007.00868.x

[4] Imran M, Mahmood S. An overview of animal prion diseases. Vetrol J 2011; 8:493; PMID:22044871; http://dx.doi.org/10.1186/1743-422X-8-493

[5] Fields BN, Knipe DM, Howley PM. Virology: Third edition. 3rd ed. New York: Lippincott-Laven Publishers; 1996.
The Prion Protein: An Overview of Its Normal Cellular (PrP^C) Function

6. Sigurdsson B, Rida A. Chronic encephalitis of sheep with general remarks on infections which develop slowly and some of their special characteristics. Br Vet J 1954; 110:341-54.

7. DeArmond S, Bouzamondo E. Fundamentals of prion biology and diseases. Toxicology 2002; 181-182:9-16; PMID:12505278; http://dx.doi.org/10.1016/S0300-483X(02)00249-4

8. Prusiner SB. Novel proteinaceous infectious particles cause scrapie. Science 1982; 216:136-144; PMID:6801762; http://dx.doi.org/10.1126/science.6801762

9. Sparks RS, Simon M, Cohn VH, Fournier R, Lem J, Klisak I, Heinzmann C, Blatt C, Lucero M, Mohandas T, et al. Assignment of the human and mouse prion protein genes to homologous chromosomes. Proc Natl Acad Sci 1986; 83:7358-7362; PMID:3094007; http://dx.doi.org/10.1073/pnas.83.19.7358

10. Meyer R, McKinley M, Bowman K, Braunfeld M, Barry R, Prusiner S. Separation and properties of cellular and scrapie prion proteins. Proc Natl Acad Sci 1986; 83:2310-2314; PMID:3085093; http://dx.doi.org/10.1073/pnas.83.19.7358

11. Kim J, Cali, Surewicz W, Kong K, Raymond Q, Atarashi G, Race R, Qing B, Gambetti L, Caughey AJ, Hof PR, Sherwood CC. Neuropil distribution in the cerebral cortex differs between humans and chimpanzees. J Comp Neurol 2012; 520(13):2917-2934; PMID:22350926; http://dx.doi.org/10.1002/jcn.23074

12. Sassa Y, Kataoka N, Inoshima Y, Ishiguro N. Anti-PrP antibodies detected at terminal stage of prion-affected mouse. Cell Immunol 2010; 263(2):212-218; PMID:20417929; http://dx.doi.org/10.1016/j.cellimm.2010.03.018

13. Pan K, Baldwin M, Nguyen J, Gasset M, Serban A, Groth D, Mehlhorn I, Huang Z, Fletterick RJ, Cohen FE. Conversion of a-helices into b-sheets features in the formation of the scrapie prion protein. Proc Natl Acad Sci 1993; 90:10962-10966; PMID:7902575; http://dx.doi.org/10.1073/pnas.90.23.10962

14. Benetti F, Legname G, De novo mammalian prion synthesis. Prion 2009; 3(4):213-9; PMID:19887900; http://dx.doi.org/10.4161/pri.3.4.10181

15. Prusiner S, McKinley M, Bowman K, Bolton D, Bendheim P, Groth D, Genser G. Scrapie prions aggregate to form amyloid-like birefringent rods. Cell 1983; 35:349-358.

16. Prusiner SB, Scott MR, DeArmond SJ, Cohen FE. Prion protein biology. Cell 1998; 93:337-348; PMID:9500169; http://dx.doi.org/10.1016/S0092-8674(98)81163-0

17. Kaneko K, Zulianello L, Scott M, Copper C, Wallace A, James T, Cohen F, Prusiner S. Evidence for protein X binding to a discontinuous epitope on the cellular prion protein during scrapie prion propagation. Proc Natl Acad Sci 1997; 94:10069-10074; PMID:9294164; http://dx.doi.org/10.1073/pnas.94.19.10069

18. Telling G, Scott M, Mastrianni J, Gabizon R, Torchia M, Cohen F, DeArmond S, Prusiner S. Prion propagation in mice expressing human and chimeric PrP transgenes implicates the interaction of cellular PrP with another protein. Cell 1995; 83(1):79-90; PMID:7553876; http://dx.doi.org/10.1016/0092-8674(95)90236-8

19. Ghetti B, Piccardo P, Frangione B, Bugiani O, Giaccone G, Young K, Prelli F, Farlow M, Dlouhy S, Tagliavini F. Prion protein amyloidosis. Brain Pathol 1996; 6(2):127-145; PMID:8737929; http://dx.doi.org/10.1111/j.1750-3639.1996.tb00796.x

20. Scott MR, Will R, Ironside J, Nguyen H-O, Tremblay P, DeArmond S, Prusiner S. Compelling transgenic evidence for transmission of bovine spongiform encephalopathy prions to humans. Proc Natl Acad Sci 1996; 96:15137-15142; http://dx.doi.org/10.1073/pnas.96.26.15137

21. Will RG, Alpers MP, Dormont D, Schonberger LB, Tateishi J. Infectious and sporadic prion diseases. In Prion Biology and Diseases. S.B. Prusiner, Edi-

22. Specoer MA, Hopkins WD, Barkes SK, Bianchi S, Hehmeyer AE, Anderson SM, Stimpson CD, Fobbs AJ, Ho PR, Sherwood CC. Neuropil distribution in the cerebral cortex differs between humans and chimpanzees. J Comp Neurol 2012; 520(13):2917-2934; PMID:22350926; http://dx.doi.org/10.1002/jcn.23074

23. Mead S, Stumpf MP, Whitfield J, Beck JA, Poulter M, Campbell T, Uphill JB, Goldstein D, Alpers M, Fisher EM, et al. Balancing selection at the prion protein gene consistent with prehistoric kurulike epidemics. Science 2003; 300(5619):640-3; PMID:12690204; http://dx.doi.org/10.1126/science.1083320

24. Heath CA, Barker RA, Esmonde TF, Harvey P, Roberts R, Trend P, Head MW, Smith C, Bell JE, Ironside JW, et al. Dura mater-associated Creutzfeldt-Jakob disease: experience from surveillance in the UK. J Neurol Neurosurg Psychiatry 2006; 77(1):80-2; PMID:16627534; http://dx.doi.org/10.1136/jnnp.2005.073395

25. Collinge J, Whitfield J, McKintosh E, Beck J, Mead S, Thomas DJ, Alpers MP. Kuru in the 21st century–an acquired human prion disease with very long incubation periods. Lancet 2006; 367(9528):2068-74; PMID:16798390; http://dx.doi.org/10.1016/S0140-6736(06)68930-7
[26] Houston F, McCutcheon S, Goldmann W, Chong A, Foster J, Sisó S, González L, Jeffrey M, Hunter N. Prion diseases are efficiently transmitted by blood transfusion in sheep. Blood 2008; 112(12):4739-4745; PMID:18647958; http://dx.doi.org/10.1182/blood-2008-04-152520

[27] Huang FP, MacPherson GG. Dendritic cells and oral transmission of prion diseases. Adv Drug Deliv Rev 2004; 56(6):901-13; PMID:15063597; http://dx.doi.org/10.1016/j.addr.2003.09.006

[28] Ironside JW, Estebeiro K, Alperovitch A, Poser S, Pocchiari M, Hofman A, Smith PG. A new variant of Creutzfeldt-Jakob disease in the UK. Lancet 1996; 347(9006):921-5; PMID:8598754; http://dx.doi.org/10.1016/S0140-6736(96)91412-9

[29] Ironside JW, McCordale L, Horsburgh A, Lim Z, Head MW. Pathological diagnosis of variant Creutzfeldt-Jakob disease. Apmis 2002; 110(1):79-87; PMID:12064259; http://dx.doi.org/10.1034/j.1600-0463.2002.100110.x

[30] Bruce ME, Will RG, Ironside JW, McConnell I, Drummond D, Suttie A, McCordale L, Chree A, Hope J, Birkett C, et al. Transmissions to mice indicate that 'new variant' CJD is caused by the BSE agent. Nature 1997; 389(6650):498-501; PMID:9333239; http://dx.doi.org/10.1038/39057

[31] Head MW. Pathological diagnosis of variant Creutzfeldt-Jakob disease. J Neurol Neurosurg Psychiatry 1994; 57(6):757-8; PMID:8006664; http://dx.doi.org/10.1136/jnnp.57.6.757

[32] Hamaguchi T, Sakai K, Noguchi-Shinohara M, Nozaki I, Takumi I, Sanjo N, Sadakane A, Nakamura Y, Kitamoto T, Saito N, et al. Insight into the frequent occurrence of dura mater graft-associated Creutzfeldt-Jakob disease in Japan. J Neurol Neurosurg Psychiatry 2013; 84(10):1171-5; PMID:23595947; http://dx.doi.org/10.1136/jnnp-2012-304850

[33] Davidson LR, Llewellyn CA, Mackenzie JM, Hewitt PE, Will RG. Variant CJD and blood transfusion: are there additional cases? Vox Sang 2014; 107(3):220-5; PMID:24916465; http://dx.doi.org/10.1111/vox.12161

[34] Billette de Villemeur T, Gelot A, Deslys JP, Dormont D, Duyckaerts C, Jardin L, Demi J, Robain O. Iatrogenic Creutzfeldt-Jakob disease in three growth hormone recipients: a neuropathological study. Neuropathol Appl Neurobiol 1994; 20(2):111-7; PMID:8072642; http://dx.doi.org/10.1111/j.1365-2990.1994.tb01169.x

[35] Delisie MB, Fabre N, Rochiccioli P, Doerr-Schott J, Rumeau JL, Bes A. [Creutzfeldt-Jakob disease after treatment with human extracted growth hormone. A clinicopathological study]. Rev Neurol (Paris) 1993; 149(10):524-7; PMID:8023064

[36] Di P, Wolf J, Collins G, DeVoe AG, Streeten B, Cowen D. Letter: Possible person-to-person transmission of Creutzfeldt-Jakob disease. N Engl J Med 1974; 290(12):693-2; PMID:4591849

[37] Brown P, Brandel JP, Preece M, Sato T. Iatrogenic Creutzfeldt-Jakob disease: the waning of an era. Neurology 2006; 67(3):389-93; PMID:16855204; http://dx.doi.org/10.1212/01.wnl.0000231528.65069.3f

[38] Brown P, Brandel JP, Sato T, Nakamura Y, MacKenzie J, Will RG, Ladogana A, Pocchiari M, Leschek EW, Schonberger LB. Iatrogenic Creutzfeldt-Jakob disease, final assessment. Emerg Infect Dis 2012; 18(6):901-7; PMID:22607808; http://dx.doi.org/10.3201/eid1806.120116

[39] Palmer CM. A week that shook the meat industry: The effects on the UK beef industry of the BSE crisis. Br Food J 1996; 98(11):17-25; http://dx.doi.org/10.1108/00070709610153650

[40] Puoti G, Bizzi A, Forlioni G, Safar JG, Gambetti P. Sporadic human prion diseases: Molecular insights and diagnosis. Lancet Neurol 2012; 11(7):618-628; PMID:22710755; http://dx.doi.org/10.1016/S1474-4422(12)70063-7

[41] Ben-Gedalya T, Cohen E. Quality control compartments coming of age. Traffic 2012; 13(5):635-642; PMID:22280095; http://dx.doi.org/10.1111/j.1600-0854.2012.01330.x

[42] Kovacs GG, Puopolo M, Ladogana A, Pocchiari M, Budka H, van Duijn C, Collins SJ, Boyd A, Giulivi A, Coulthart M, et al. Genetic prion disease: the EURO-CJD experience. Hmun Genet 2005; 118(2):166-174; PMID:16187142; http://dx.doi.org/10.1007/s00439-005-0020-1

[43] Webb TEF, Poulter M, Beck J, Uphill J, Adamson G, Campbell T, Linehan J, Powell C, Brandner S, Pal S, et al. Phenotypic heterogeneity and genetic modification of P102L inherited prion disease in an international series. Brain 2008; 131:2632-2646; PMID:18757886; http://dx.doi.org/10.1093/brain/awn202
The Prion Protein: An Overview of Its Normal Cellular (PrPc) and Abnormal Prion (PrPSc) Forms

[46] Arata H, Takashima H, Hirano R, Tomimitsu H, Machigashira K, Izumi K, Kikuno M, Ng AR, Umehara F, Arisato T, et al. Early clinical signs and imaging findings in Gerstmann-Straussler-Scheinker syndrome (Pro102Leu). Neurology 2006; 66(11):1672-1678; PMID:16769939; http://dx.doi.org/10.1212/01.wnl.0000218211.85675.18

[47] Yamada M, Tomimitsu H, Yokota T, Tomi H, Sunohara N, Mukoyama M, Itoh Y, Suematsu N, Otomo E, Okeda R, et al. Involvement of the spinal posterior horn in Gerstmann-Straussler-Scheinker disease (PrP P102L). Neurology 1999; 52(2):260-265; PMID:9932941; http://dx.doi.org/10.1212/WNL.52.2.260

[48] Kovacs GG, Trabattoni G, Hainfellner JA, Ironside JW, Knight RS, Budka H. Mutations of the prion protein gene - phenotypic spectrum. J Neurol 2002; 249(11):1567-1582; PMID:12420099; http://dx.doi.org/10.1007/s00415-002-0896-9

[49] Kretzschmar HA, Kufer P, Riethmüller G, DeArmond S, Prusiner SB, Schiffer D. Prion protein mutation at codon-102 in an Italian family with gerstmann-straussler-scheinker syndrome. Neurorlogy 1992; 42(4):809-810; PMID:1348851; http://dx.doi.org/10.1212/WNL.42.4.809

[50] Rowe DB, Lewis V, Needham M, Rodriguez M, Boyd A, McLean C, Roberts H, Masters CL, Collins SJ. Novel prion protein gene mutation presenting with subacute PSP-like syndrome. Neurology 2007; 68(11):868-870; PMID:17353478; http://dx.doi.org/10.1212/01.wnl.0000256819.61531.98

[51] Hsiao K, Baker HF, Crow TJ, Poulter M, Owen F, Terwilliger JD, Westaway D, Ott J, Prusiner SB. Linkage of a Prion Protein Missense Variant to Gerstmann-Straussler Syndrome. Nature 1989; 338(6213):342-345; PMID:2564168; http://dx.doi.org/10.1038/338342a0

[52] Kretzschmar HA, Honold G, Seitelberger F, Feucht M, Wessely P, Mehraein P, Budka H. Prion Protein Mutation in Family 1st Reported by Gerstmann, Straussler, and Scheinker. Lancet 1991; 337:8750; 1160-1160; PMID:1674033; http://dx.doi.org/10.1016/0140-6736(91)92826-N

[53] Aguzzi A, Calella AM. Prions: Protein aggregation and infectious diseases. Physiol Rev 2009; 89 (4):1105-1152; PMID:19789378; http://dx.doi.org/10.1152/physrev.00006.2009

[54] Montagnese F, Barca E, Musumeci O, Mondello S, Migliorato A, Ciranni A, Rodolico C, De Filippi P, Danesino C, Toscano A. Clinical and molecular aspects of 30 patients with late-onset Pompe disease (LOPD): Unusual features and response to treatment. J Neuro 2015; 262(4):968-978; PMID:25673129; http://dx.doi.org/10.1007/s00415-015-7664-0

[55] Hinnell C, Coulthart MB, Jansen GH, Cashman NR, Lauzon J, Clark A, Costello F, White C, Midha R, Wiebe S, et al. Gerstmann-Straussler-Scheinker disease due to a novel prion protein gene mutation. Neurology 2011; 76(5):485-487; PMID:21282596; http://dx.doi.org/10.1212/WNL.0b013e31820a0ab2

[56] Riudavets MA, Sraka MA, Schultz M, Rojas E, Martinetto H, Begue C, de Halac IN, Poleggi A, Equestre M, Pocchiari M, et al. Gerstmann-Straussler-Scheinker syndrome with variable phenotype in a new kindred with PRNP-P102L Mutation. Brain Pathol 2014; 24(2):142-147; PMID:23944754; http://dx.doi.org/10.1111/bpa.12083

[57] White A, Enever P, Tayebi M, Mushens R, Linehan J, Brandner S, Anstee D, Collinge J, Hawke S. Monoclonal antibodies inhibit prion replication and delay the development of prion disease. Nature; 2003 422(6927):80-3; PMID:12621436; http://dx.doi.org/10.1038/nature01457

[58] Perrier V, Solassol J, Crozet C, Frobert Y, Mouton-Gilles C, Grassi J, Lehmann S. Anti-PrP blockers and PrPSc replication in prion-infected cell cultures by accelerating PrPc degradation. J Neurochem 2004; 89:454-463; PMID:15056288; http://dx.doi.org/10.1111/j.1471-4159.2004.02356.x

[59] Korth C, May B, Cohen F, Prusiner S. Acidine and phenothiazine derivatives as pharmacotherapeutics for prion disease. Proc Natl Acad Sci 2001; 98(17):9836-41; PMID:11504948; http://dx.doi.org/10.1073/pnas.161274798

[60] Korth C, Peters P. Emerging pharmacotherapies for Creutzfeld–Jakob disease. Arch Neurol 2006; 63(4):497-501; PMID:16606761; http://dx.doi.org/10.1001/archneur.63.4.497

[61] Doh-Ura K, Iwaki T, Caughey B. Lysosomotropic agents and cysteine protease inhibitors inhibit scrapie-associated prion protein accumulation. J Virol 2000; 74(10):4894-4897; PMID:10775631; http://dx.doi.org/10.1128/JVI.74.10.4894-4897.2000

[62] Barrett A, Tagliavini F, Forloni G, Salmona M, Colombo L, Luigi D, Limido L, Suardi S, Rossi G, Auvre F, et al. Evaluation of quinacrine treatment and imaging findings in Gerstmann-Straussler-Scheinker syndrome. Brain Pathol 2014; 24(2):142-147; PMID:23944754; http://dx.doi.org/10.1111/bpa.12083

[63] Hassler R, Topakian R, Weis S, Rahimi J, Trenkler J, Hulteberg R, Aboulenein-Djamshidian F, Ströbel T, Budka H, Yull H, et al. A case of variably protease-sensitive prionopathy treated with doxycycline. J Neurol Neurosurg Psychiatry 2015; 86(7):816-8; PMID:25575846; http://dx.doi.org/10.1136/jnnp-2014-309871

[64] Haik S, Marcon G, Mallet A, Tettamanti M, Welteratne A, Giaccone G, Azimi S, Pietrini V, Fabreguettes JR, Imperiale D, et al. Doxycycline in Creutzfeldt-Jakob disease: a phase 2, randomised,
double-blind, placebo-controlled trial. Lancet Neurol 2014; 13(2):150-8; PMID:24411709; http://dx.doi.org/10.1016/S1474-4422(13)70307-7

[65] Vetrugno V, Puopolo M, Cardone F, Capozzoli F, Lodagana A, Pacchiari M. The future for treating Creutzfeldt–Jakob disease. Exp Opin Orphan Drugs 2015; 3(1):57-74; http://dx.doi.org/10.1017/21678707.2015.994605

[66] Forloni G, Artuso V, Roiter I, Morbin M, Tagliafini F. Therapy in prion diseases. Curr Top Med Chem 2013; 13(19):2465-76; PMID:24059336; http://dx.doi.org/10.2174/1568026611316660173

[67] Forloni G, Tettamanti M, Lucca U, Albanese Y, Quaglio E, Chiesa R, Erbetta A, Villani F, Redaelli V, Tagliafini F, et al. Preventive study in subjects at risk of fatal familial insomnia: Innovative approach to rare diseases. Prion 2015; 9(2):75-9; PMID:25996399; http://dx.doi.org/10.1080/19336896.2015.1027857

[68] Rigter A, Bossers A. Sheep scrapie susceptibility-linked polymorphisms do not modulate the initial binding of cellular to disease-associated prion protein prior to conversion. J Gen Virol 2005; 86(Pt 9):2627-34; PMID:16099922; http://dx.doi.org/10.1099/vir.0.80901-0

[69] Horiiuchi M, Priola SA, Chabry J, Caughey B. Interactions between heterologous forms of prion protein: binding, inhibition of conversion, and species barriers. Proc Natl Acad Sci U S A 2000; 97(11):5836-41; PMID:10811921; http://dx.doi.org/10.1073/pnas.110523897

[70] Priola SA, Vorberg I. Molecular aspects of disease pathogenesis in the transmissible spongiform encephalopathies. Methods Mol Biol 2004; 268:517-40; PMID:15156065

[71] Skinner PJ, Kim HO, Bryant D, Kinzel NJ, Reilly Priola SA, Ward AE, Goodman PA, Olson K, Seelig DM. Treatment of prion disease with heterologous prion proteins. PLoS One 2015; 10(7):e0131993; PMID:26134409; http://dx.doi.org/10.1371/journal.pone.0131993

[72] Westergard L, Christensen H, Harris D. The cellular prion protein (PrPC): Its physiological function and role in disease. Vet Res 2007; 38(4):629-644.

[73] Du J, Pan Y, Shi Y, Guo C, Jin X, Sun L, Liu N, Qiao T, Fan D. Overexpression and significance of prion protein in gastric cancer and multidrug-resistant gastric carcinoma cell line SGC7901/ADR. Int J Cancer 2005; 113(2):213-20; PMID:15386405; http://dx.doi.org/10.1002/ijc.20570

[74] Vey M, Pilkuhn S, Wille S, Nixon R, DeArmond S, Smart E, Taraboulos A, Prusiner S. Subcellular colocalization of the cellular and scrapie prion proteins in caveolae-like membrane domains. PNAS 1996; 93(25):14945-14949; PMID:8962161; http://dx.doi.org/10.1073/pnas.93.25.14945

[75] Alfonso DS, Adriana Z, Philippe D. Structural and hydration properties of the partially Unfolded States of the prion protein. Biophys J 2007; 93(4):1284-92; PMID:17483173; http://dx.doi.org/10.1529/biophysj.107.108613

[76] Mehrpour M, Codogno P, From physiology to cancer biology. Cancer Lett 2010; 290(1):23; http://dx.doi.org/10.1016/j.canlet.2009.07.009

[77] Linden R, Martins V, Prado M, Cammarota M, Izquiero I, Brentani R. Physiology of the prion protein. Physiol Rev 2008; 88:673-728; PMID:18391177; http://dx.doi.org/10.1152/physrev.00007.2007

[78] Stewart R, Harris D. Mutational analysis of topological determinants in prion protein (PrP) and measurement of transmembrane and cytosolic PrP during prion infection. J Biol Chem 2003; 278:45960-45968; PMID:12933795; http://dx.doi.org/10.1074/jbc.M307833200

[79] Welker E, Raymond LD, Scheraga HA, Caughey B. Intramolecular versus intermolecular disulfide bonds of the cellular prion protein in neural and non-neural tissues. J Biol Chem 2002 277(36):33477-81; PMID:12082114; http://dx.doi.org/10.174/jbc.M204273200

[80] Hooper N. Roles of proteolysis and lipid rafts in the processing of the amyloid precursor protein and prion protein. Biochem Soc Trans 2005; 33:335-338; http://dx.doi.org/10.1042/BST0330335

[81] Mange A, Beranger F, Poock K, Onodera T, Frobert Y, Lehmann S. Alpha- and beta-cleavages of the amino-terminus of the cellular prion protein. Biol Cell 2004; 96:125-132; PMID:15050367; http://dx.doi.org/10.1042/BST0330335

[82] Vincent B, Palet E, Frobert Y, Lehmann S, Grassi J, Checler F. Phorbol ester-regulated cleavage of normal prion protein in HEK293 human cells and murine neurons. J Biol Chem 2000; 275:35612-35616; PMID:10952979; http://dx.doi.org/10.1074/jbc.M004628200

[83] Pan K, Stahl N, Prusiner S. Purification and properties of the cellular prion protein from Syrian hamster brain. Protein Sci 1992; 1:1343-1352; PMID:1363897; http://dx.doi.org/10.1016/j.biolcel.2003.11.007

[84] Jimenez-Huete A, Lievens P, Vidal R, Piccardo P. Direct interaction of the cellular and scrapie prion protein in caveolae-like membrane domains. PNAS 1996; 93(25):14945-14949; PMID:8962161; http://dx.doi.org/10.1073/pnas.93.25.14945
THE PRION PROTEIN: AN OVERVIEW OF ITS NORMAL CELLULAR (PrPc)
Vassallo N, Herms J, Behrens C, Krebs B, Saeki K, Onodera T, Windl O, Kretzschmar HA. Activation of phosphatidylinositol 3-kinase by cellular prion protein and its role in cell survival. Biochem Biophys Res Commun 2005; 332(1):75-82; PMID:15896301; http://dx.doi.org/10.1016/j.bbrc.2005.04.099

Chiarini LB, Freitas AR, Zanata SM, Brentani RR, Martins VR, Linden R. Cellular prion protein transduces neuroprotective signals. Embo J 2002; 21(13):3317-26; PMID:12093733; http://dx.doi.org/10.1093/emboj/cdf324

Mouillet-Richard S, Ermonval M, Chebassier C, Laplanche JL, Lehmann S, Launay JM, Kellermann O. Signal transduction through prion protein. Science 2000; 289(5486):1925-8; PMID:10988071; http://dx.doi.org/10.1126/science.289.5486.1925

Mattei V, Garofalo T, Misasi R, Circella A, Manganeli V, Lucania G, Pavan A, Sorice M. Prion protein is a component of the multimolecular signalling complex involved in T cell activation. FEBS Lett 2004; 560(1-3):14-8; PMID:15539455; http://dx.doi.org/10.1016/S0014-5793(04)00029-8

Martinez D, Lopez-Bravo M, Metharom P, Ardavin C, Accourtier P. Prion protein expression by mouse dendritic cells is restricted to the nonplasmacytoid subsets and correlates with the maturation state. J Immunol 2006; 177(9):6137-42; PMID:17056541; http://dx.doi.org/10.4049/jimmunol.177.9.6137

McCulloch L, Brown KL, Mabbott 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; PMID:23121447; http://dx.doi.org/10.1111/jimm.12031

de Almeida CJ, Chiarini LB, da Silva JP, E Silva PM, Martins MA, Linden R. The cellular prion protein modulates phagocytosis and inflammatory response. J Leukoc Biol 2005; 77(2):238-46; PMID:15539455; http://dx.doi.org/10.1189/jlb.1103531

Bainbridge J, Walker K. The normal cellular form of prion protein modulates T cell responses. Immunol Lett 2005; 96(1):147-50; PMID:15885317; http://dx.doi.org/10.1016/j.imlet.2004.08.006

Seong YJ, Sung PS, Jang YS, Choi YJ, Park BC, Park SH, Park YW, Shin EC. Activation of human natural killer cells by the soluble form of cellular prion protein. Biochem Biophys Res Commun 2015; 464(2):512-8; PMID:26159919; http://dx.doi.org/10.1016/j.bbrc.2015.06.172

Buehler H, Fischer M, Lang Y, Bluethmann H, Lipp H, DeArmond S, Prusiner S, Aguet M, Weissmann C. Normal development and behaviour of mice lacking the neuronal cell surface PrP protein. Nature 1992; 356:577-582; PMID:1373228; http://dx.doi.org/10.1038/356577a0

Kuwahara C, Takeuchi A, Nishimura T, Haraguchi K, Kubosaki A, Matsumoto Y, Saeki K, Matsumoto Y, Yokoyama T, Itohara S, et al. Prions prevent neuronal cell-line death. Nature 1999; 400(6741):225-6; PMID:10421360; http://dx.doi.org/10.1038/22241

Roucou X, Gains M, LeBlanc A. Neuroprotective functions of prion protein. J Neurosci Res 2004; 75(2):153-61; PMID:14705136; http://dx.doi.org/10.1002/jnr.10864

Bounhar Y, Zhang Y, Goodyer C, LeBlanc A. Prion protein protects human neurons against Bax-mediated apoptosis. J Biol Chem 2001; 276(42):39145-9; PMID:11522774; http://dx.doi.org/10.1074/jbc.C100443200

Martinou J, Green D. Breaking the mitochondrial barrier. Nat Rev Mol Cell Biol 2001; 2(1):63-7; PMID:11413467; http://dx.doi.org/10.1038/35048069

Roucou X, LeBlanc A. Cellular prion protein neuroprotective function: implications in prion diseases. J Mol Med 2005; 83(3-11); PMID:15645198; http://dx.doi.org/10.1007/s00109-004-0605-5

Collinge J, Whittington M, Sidle K, Smith C, Palmer M, Clarke A, Jefferys J. Prion protein is necessary for normal synaptic function. Nature 1994; 370:295-297; PMID:8035877; http://dx.doi.org/10.1038/370295a0

Colling S, Collinge J, Jefferys J. Hippocampal slices from prion protein null mice: disrupted Ca(2+) -activated K+ currents. Neurosci Lett 1996; 209:49-52; PMID:8734907; http://dx.doi.org/10.1016/0304-3940(96)12596-9

Curtis J, Errington M, Bliss T, Voss K, MacLeod N. Age dependent loss of FTD and LTP in the hippocampus of PrP-null mice. Neurobiol Dis 2003; 13:55-62; PMID:12758067; http://dx.doi.org/10.1016/S0969-9961(03)00017-2

Mallucci GR, Ratte S, Asante EA, Linehan I, Goward I, Jefferys JGR, Collinge J. Post-natal knock-out of prion protein alters hippocampal CA1 properties, but does not result in neurodegeneration. EMBO J 2002; 21:202-210; PMID:11823413; http://dx.doi.org/10.1093/emboj/21.3.202

Manson JC, Hope J, Clarke AR, Johnston A, Black C, MacLeod N. PrP gene dosage and long term potentiation. Neurodegeneration 1995; 4:113-114; PMID:7600180; http://dx.doi.org/10.1006/neur.1995.0014
[126] Criado J, Sanchez-Alavez M, Conti B, Giacchino J, Wills D, Henrikson S, Race R, Manson J, Chesebro B, Oldstone M. Mice devoid of prion protein have cognitive deficits that are rescued by reconstitution of PrP in neurons. Neurobiol Dis 2005; 19:255-265; PMID:15837581; http://dx.doi.org/10.1016/j.nbd.2005.01.001

[127] Lobao-Soures B, Walz R, Carlotti Jr. C, Sakamoto A, Calfo F, Terzian A, da Silva J, Wichert-Ana L, Coimbra N, Bianchini M. Cellular prion protein regulates the motor behaviour performance and anxiety-induced responses in genetically modified mice. Behav. Brain Res 2007; 183:87-94; PMID:17618696; http://dx.doi.org/10.1016/j.bbr.2007.05.027

[128] Mange A, Milhavet O, Umlauf D, Harris D, Lehmann S. PrP dependent cell adhesion in N2a neuroblastoma cells. FEBS Lett 2002; 514(2-3):159-62; PMID:11943143; http://dx.doi.org/10.1016/S0014-5793(02)02338-4

[129] Crossin K, Krushel L. Cellular signaling by neural cell adhesion molecules of the immunoglobulin superfamily. Dev Dyn 2000; 218:260-279; PMID:10842356; http://dx.doi.org/10.1002/(SICI)1097-0177(200006)218:2<260::AID-DVDY3>3.0.CO;2-9

[130] Ronn L, Berezin V, Bock E. The neural cell adhesion molecule in synaptic plasticity and ageing. Int J Dev Neurosci 2000; 18:193-199; PMID:10715574; http://dx.doi.org/10.1016/S0736-5748(99)00088-X

[131] Schachner M. Neural recognition molecules and synaptic plasticity. Curr Opin Cell Biol 1997; 9:627-634; PMID:9330865; http://dx.doi.org/10.1016/S0955-0674(97)80115-9

[132] Santuccione A, Sytnyk V, Leshchyns’ka I, Schachner M. Prion protein recruits its neuronal receptor NCAM to lipid rafts to activate p95fyn and to enhance neurite outgrowth. J Cell Biol 2005; 169(2):341-54; PMID:15851519; http://dx.doi.org/10.1083/jcb.200409127

[133] Chen S, Mange A, Dong L, Lehmann S, Schachner M. Prion protein as trans-interacting partner for neurons is involved in neurite outgrowth and neuronal survival. Mol Cell Neurosci 2003; 22(2):227-33; PMID:12676532; http://dx.doi.org/10.1016/S1044-7311(02)00014-3

[134] Liang J, Pan YL, Ning XX, Sun LJ, Lan M, Hong L, Du JP, Liu N, Liu CJ, Qiao TD, et al. Overexpression of PrPC and its antiapoptosis function in gastric cancer. Tumour Biol 2006; 27(2):84-91; PMID:16582585; http://dx.doi.org/10.1159/000092488

[135] Liang J, Pan Y, Zhang D, Guo C, Shi Y, Wang J, Chen Y, Wang X, Liu J, Guo X, et al. Cellular prion protein promotes proliferation and G1/S transition of human gastric cancer cells SGC7901 and AGS. FASEB J 2007; 21(9):2247-56; PMID:17409275; http://dx.doi.org/10.1096/fj.06-7799com

[136] Han H, Bearss D, Browne W, Calaluce R, Nagle R, Hoff D. Identification of differentially expressed genes in pancreatic cancer cells using cDNA microarray. Cancer Res 2002; 62:2890-2896; PMID:12019169

[137] Li C, Yu S, Nakamura F, Yin S, Xu J, Petrolla AA, Singh N, Tartakoff A, Abbott DW, Xin W, et al. Binding of pro-prion to filamin A disrupts cytoskeleton and correlates with poor prognosis in pancreatic cancer. J Clin Invest 2009; 119(9):2725-36; PMID:19690385; http://dx.doi.org/10.1172/JCI39542

[138] Antonacopoulou AG, Grivas PD, Skarlas L, Kalofonos M, Scopa CD, Kalofonos HP. POLR2F, ATP6V0A1 and PRNP expression in colorectal cancer: new molecules with prognostic significance? Anticancer Res 2008; 28(2B):1221-7; PMID:18505059

[139] Antonacopoulou AG, Palli M, Marousi D, Dimitrakopoulos F, Kyriakopoulou L, Tsimandas AC, Scopa CD, Papavassiliou AG, Kalofonos HP. Prion protein expression and the M129V polymorphism of the PRNP gene in patients with colorectal cancer. Mol Carcinog 2010; 49(7):693-9; PMID:20564346

[140] Zhao Y, You H, Liu F, An H, Shi Y, Yu Q, Fan D. Differentially expressed gene profiles between multidrug resistant gastric adenocarcinoma cells and their parental cells. Cancer Lett 2002; 185(2):211-8; PMID:12169395; http://dx.doi.org/10.1016/S0304-3835(02)00264-1

[141] Wang Q, Qian J, Wang F, Ma Z. Cellular prion protein accelerates colorectal cancer metastasis via the Fyn-SP1-SATB1 axis. Oncol Rep 2012; 28(6):2029-34; PMID:22972305

[142] Han H, Bearss D, Browne W, Calaluce R, Nagle R, Hoff D. Identification of differentially expressed genes in pancreatic cancer cells using cDNA microarray. Cancer Res 2002; 62:2890-2896; PMID:12019169

[143] Han H, Bearss D, Browne W, Calaluce R, Nagle R, Hoff D. Identification of differentially expressed genes in pancreatic cancer cells using cDNA microarray. Cancer Res 2002; 62:2890-2896; PMID:12019169

[144] Duffy M, Maguire T, Hill A, McDermott E, O’Higgins N, Metalloproteinases: role in breast carcinogenesis, invasion and metastasis. Breast Cancer Res 2000; 2:252-257; PMID:11250717; http://dx.doi.org/10.1016/j.bcr.2007.05.027

[145] Popova SN, Tarvainen I, Capellari S, Parchi P, Hannikainen P, Pirinen M, Scopa CD, Kalofonos HP. POLR2F, ATP6V0A1 and PRNP expression in colorectal cancer: new molecules with prognostic significance? Anticancer Res 2008; 28(2B):1221-7; PMID:18505059

[146] Han H, Bearss D, Browne W, Calaluce R, Nagle R, Hoff D. Identification of differentially expressed genes in pancreatic cancer cells using cDNA microarray. Cancer Res 2002; 62:2890-2896; PMID:12019169

[147] Han H, Bearss D, Browne W, Calaluce R, Nagle R, Hoff D. Identification of differentially expressed genes in pancreatic cancer cells using cDNA microarray. Cancer Res 2002; 62:2890-2896; PMID:12019169

[148] Han H, Bearss D, Browne W, Calaluce R, Nagle R, Hoff D. Identification of differentially expressed genes in pancreatic cancer cells using cDNA microarray. Cancer Res 2002; 62:2890-2896; PMID:12019169

[149] Han H, Bearss D, Browne W, Calaluce R, Nagle R, Hoff D. Identification of differentially expressed genes in pancreatic cancer cells using cDNA microarray. Cancer Res 2002; 62:2890-2896; PMID:12019169
phenotype in a Gerstmann-Straussler-Scheinker P102L family. Acta Neurol Scand 2012; 126 (5):315-323; PMID:22211828; http://dx.doi.org/10.1111/j.1600-0404.2011.01628.x

[146] Burns A, Iliffe S. Alzheimer’s disease. 2009; 338.

[147] Peters C, Espinoza MP, Gallegos S, Opazo C, Aguayo LG. Alzheimer’s Abeta interacts with cellular prion protein inducing neuronal membrane damage and synaptotoxicity. Neurobiol Aging 2015; 36(3):1369-77; PMID:25599875; http://dx.doi.org/10.1016/j.neurobiolaging.2014.11.019

[148] Aimi T, Suzuki K, Hoshino T, Mizushima T. Dextran sulfate sodium inhibits amyloid-beta oligomer binding to cellular prion protein. J Neurochem 2015; 134(4):611-7; PMID:25963375; http://dx.doi.org/10.1111/jncl.13166

[149] Ownby RL, Crocco E, Acevedo A, John V, Loewenstein D. Depression and risk for Alzheimer disease: systematic review, meta-analysis, and metaregression analysis. Arch Gen Psychiatry 2006; 63(5):530-8; PMID:16651510; http://dx.doi.org/10.1001/archpsyc.63.5.530

[150] Green RC, Cupples LA, Kurz A, Auerbach S, Go R, Sadovnick D, Duara R, Kukull WA, Chui H, Edeki T, et al. Depression as a risk factor for Alzheimer disease: the MIRAGE Study. Arch Neurol 2003; 60(5):753-9; PMID:12756140; http://dx.doi.org/10.1001/archneur.60.5.753

[151] Thompson A, MacKay A, Rudge P, Lukic A, Porter MC, Lowe J, Collinge J, Mead S. Behavioral and psychiatric symptoms in prion disease. Am J Psychiatry 2014; 171(3):265-74; PMID:24585329; http://dx.doi.org/10.1176/appi.ajp.2013.12111460

[152] Gadotti VM, Bonfield SP, Zamponi GW. Depressive-like behaviour of mice lacking cellular prion protein. Behav Brain Res 2012; 227(2):319-23; PMID:21439331; http://dx.doi.org/10.1016/j.bbr.2011.03.012

[153] Beckman D, Santos LE, Americo TA, Ledo JH, de Mello FG, Linden R. Prion protein modulates monoaminergic systems and depressive-like behavior in mice. J Biol Chem 2015; 290(33):20488-98; PMID:26152722

[154] Ledo JH, Azevedo EP, Clarke JR, Ribeiro FC, Figueiredo CP, Fogueiro D, De Felice FG, Ferreira ST. Amyloid-beta oligomers link depressive-like behavior and cognitive deficits in mice. Mol Psychiatry 2013; 18(10):1053-4; PMID:23183490; http://dx.doi.org/10.1038/mp.2012.168