Prion Diseases: the link between neurodegeneration and protein misfolding

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Abstract

Prion diseases are neurodegenerative diseases characterised by misfolding of the prion proteins in the brain. During the misfolding process, the prions change its conformation from the normally functioning cellular prion protein (PrP^{C}) into the pathogenic scrapie-associated prion protein (PrP^{Sc}). PrP^{Sc} can cause transmissible spongiform encephalopathies (TSE), which prion diseases are also known as. Misfolding and accumulation of the PrP^{C} causes spongiform neurodegeneration in the brain. Examples of human prion diseases are Creutzfeldt-Jakob Disease (CJD), kuru, and Gerstmann-Sträussler-Scheinker disease (GSS). Animal examples of prion diseases are Bovine spongiform encephalopathy (BSE), also known as mad cow disease, Chronic Wasting Disease (CWD) and Scrapie, found in cattle, cervids and sheep or goats respectively. Prion diseases have different aetiologies. It can originate from spontaneous misfolding, a genetic mutation, or from infection from contamination of food or surgical equipment. The main underlying mechanisms in neurodegeneration are protein aggregation and neuroinflammation, however not all underlying mechanisms of prion diseases are yet fully understood. Its role in Cu^{2+} binding is not broadly elucidated and its role in reactive oxygen species is also yet to be fully understood. Despite not being fully understood, prion diseases do show similarities with other neurodegenerative disorders. Alzheimer's disease and Huntington's disease also form protein aggregates and cause neuroinflammation that impairs cell function, causing neurodegeneration in the end.

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What are characteristics of prion diseases?

Prion diseases can be subcategorised into 3 groups, this division is based on the aetiology of the disease. The first group is characterised by a sporadic origin of pathology. The second group is characterised by the disease being caused by the presence of a genetic mutation in the gene encoding for PrP^{C}. The last group is characterised by the acquisition of the disease via misfolded prions that do not originate from the organism itself (Bernardi L, et al (2019)).

One of the prion diseases is CJD. CJD can be placed in all three categories based on the variant of CJD. It can be divided into one of the following 4 variants: Sporadic CJD (sCJD), familial/genetic CJD (f/gCJD), Iatrogenic CJD (iCJD), and variant CJD (vCJD).

It is estimated that 1,5 patients per million from 2003 to 2015 in the United States is diagnosed with CJD (Elziny MM, Elsaid SS (2022)). sCJD is the most prevalent variant, affecting up to 90% of all people suffering from CJD. The mean onset of disease is at age 62, although much younger and older cases have been reported. The average survival of sCJD is 4 to 8 months, with 90% of the patients dying within a year of diagnosis (Imran M, Mahmood S (2011)). sCJD is caused by a spontaneous misfolding of PrP^{C} into PrP^{Sc}. PrP^{Sc} spreads throughout the brain and initiates the conformational changes of PrP^{C} into PrP^{Sc}, resulting in accumulation of PrP^{Sc} throughout the brain. This accumulation of PrP^{Sc} causes spongiform neurodegeneration, neuronal loss and gliosis. Gliosis is the process

in which glial cells change in reactivity due to central nervous system (CNS) damage. In some cases, amyloid plaques are found. The main clinical symptom that presents itself is dementia, this can be slow or rapidly progressive. Other clinical symptoms are spontaneous or induced myoclonia, (extra)pyramidal dysfunction and behavioural symptoms. In prolonged disease progression akinetic mutism develops.

f/gCJD is the second most prevalent type of CJD, with an estimated occurrence of 10-15% of all CJD cases (Imran M, Mahmood S (2011)). A mutation in the PRNP gene causes an increased risk of the conformational change of PrP^{C} into PrP^{Sc}. This mutation can be inherited; therefore, it is called familial CJD. The penetrance is highly variable with mutations, resulting in a more variable disease manifestation. More than half of the cases reported does not have a positive family history with the disease, therefore the term genetic CJD is also used for the same cases. The clinical symptoms presented in patients with f/gCJD are in most cases similar to sCJD, since the mutation is increasing the risk of protein misfolding. However certain specific mutations are known to cause different symptoms.

Another prion disease with a genetic aetiology is GSS. GSS is an inherited prion disorder that is characterised by mutations in the PRNP gene and misfolding of PrP^{C}. The misfolded PrP^{Sc} contains fragments that are rich in β-sheets that are protease resistant. Gliosis, neuronal loss, and spongiform degeneration can be found in GSS (Pirisinu L, et al, (2016)).

Iatrogenic CJD is characterised by the transmission of PrP^{C} to a healthy individual via a medical procedure. For example: contaminated neurosurgical instruments, cadaveric grafts, or intramuscular injection of growth hormone or gonadotrophin hormone derived from an infected pituitary gland. The first case of iCJD was established in 1974 (Imran M, Mahmood S (2011)). A cadaveric corneal transplant from a CJD patient was the cause of the transfer of the disease. Most cases of iCJD can be linked to treatment with human growth hormone and Lyodura grafts. Lyodura grafts were made from cadaveric dura mater tissue harvested via autopsy. The use of the Lyodura grafts in Japan caused the occurrence of over 150 cases of iCJD between 1975 and 2017(Ae R, et al (2018)). The use of growth hormone between 1950s and 1985 in about 30,000 children has led to an estimated 1/100 prevalence of iCJD in this population. Before the growth hormone was produced via recombinant DNA methods, large batches of cadaveric pituitary glands were used to extract the hormone. It is most likely the presence of a few pituitary glands originating from people suffering from CJD that caused contamination of the grafts used in treatment. iCJD cases linked to dura mater grafts are similar in pathology to sCJD, while iCJD linked to growth hormone treatment is more similar to kuru in pathology.

Kuru is a prion disease that can only be found in the Fore linguistic group of Papua New Guinea Eastern Highlands. These people acquired the disease via cannibalistic rituals in which they eat parts of the brain of deceased people as a mourning process. The

symptoms found in kuru include ataxia, tremors, and dementia. However distinctive for kuru is the presence of kuru plaques, spherical bodies found in the brain.

vCJD is a variant of CJD in which the disease is obtained via contamination with BSE (Belay ED (1999)) (Prusiner SB (1998)). Big outbreaks of BSE in the UK were linked to a surge in CJD cases. The typical neurological symptoms in vCJD are comparable to sCJD and include cerebellar ataxia, cognitive impairment and akinetic mutism (Imran M, Mahmood S (2011)). These neurological symptoms are preceded by psychiatric symptoms, which may include emotional lability, insomnia, agitation, or paranoid delusion. However, there is individual variation in clinical phenotype. vCJD is characterised by the presence of plagues, which have similarities to kuru-plaques, in the basal ganglia, thalamus and can be spread over the cerebral cortex. These kuru-like plagues are surrounded by spongiform lesions.

What are prions?

PrP^C is shown to be involved in many different processes, although the precise function is not well defined. PrP^C is encoded by the PRNP gene located on chromosome 20 in humans, in mice it is chromosome 2. The encoding region is located in the last of two or three exons, depending on the species looked at. The PrP^C is an anchored glycosylphosphatidylinositol (GPI) protein located at the cell membrane. It has two N-linked glycosylation sites near the C-terminal, in these sites a carbohydrate is bound to nitrogen, asparagine or arginine sidechains. PrP^C is mainly presented as a di-glycosylated protein. The C-terminal also contains a disulfide bond. The protein is on average 210 amino acids long and has a well conserved globular structure at the C-terminal. This globular structure consists of three α helices and a short β-sheet. The tertiary structure of the N-terminal is less defined.

The N-terminal consists of an octa repeat sequence that is able to bind Cu^{2+}. The repeat consists of the following amino acids: PHGGGWGQ. This octa repeat is 4 or 5 times present and each HGGGW segment is able to bind a single CU^{2+}. These copper bindings are forming a pentacoordinate complex with the HGGGW segments (Chattopadhyay M, et al (2005)).

PrP^C can be processed in two manners, cleaving and shedding. Cleavage occurs after ingestion of the PrP^C. Cleaving the N-terminal results in the C-terminal to stay attached to the membrane. The size of the fragment released is dependent on the type of cleavage. α-cleavage and β-cleavage takes place at the N-terminus, as can be seen in

Figure 1. This mainly happens during the vesicular trafficking of PrP^C. α-cleavage is not exclusive to a single enzyme, it allows for variation in sequence as long as the hydrophobic properties of the cleaving site are respected. The cleaving products are called N1 which is approximately 11kDa in size and C1 which is approximately 18kDa in size and stays attached to the membrane. In humans it is found that ADAM10 and ADAM17 cleave PrPC, however ADAM17 needs to be stimulated to get active (Kovač V, Čurin Šerbec V (2022)). ADAM8 performs α-cleavage in the muscles. Research has shown that the absence of α-cleavage results in a toxic environment. At the end of the octa repeated region of PrP^C β-cleavage takes place. It forms the fragments N2 which is approximately 9kDa in size and C2 which is approximately 20kDa in size (Altmeppen HC, et al (2012)). ADAM8 is one of the enzymes that can perform β-cleavage, but reactive oxygen species (ROS) are also capable of inducing β-cleavage. β-cleavage is thought to be protective against oxidative stress, which plays a role in the pathology of prion diseases.

γ-cleavage and shedding are the processing of PrP^C at the C-terminal of the protein, as can be seen in Figure 1. This process happens at the membrane where PrP^C is anchored. γ-cleavage creates two fragments, the N3 fragment approximately 20kDa in length and the GPI-anchored C3 fragment approximately 5kDa in length (Kovač V, Čurin Šerbec V (2022)). The precise role of γ-cleavage has not been found yet, however data suggest that C3 fragments present in CJD brains may play an important role in its pathogenicity (Lewis, et al (2016)).

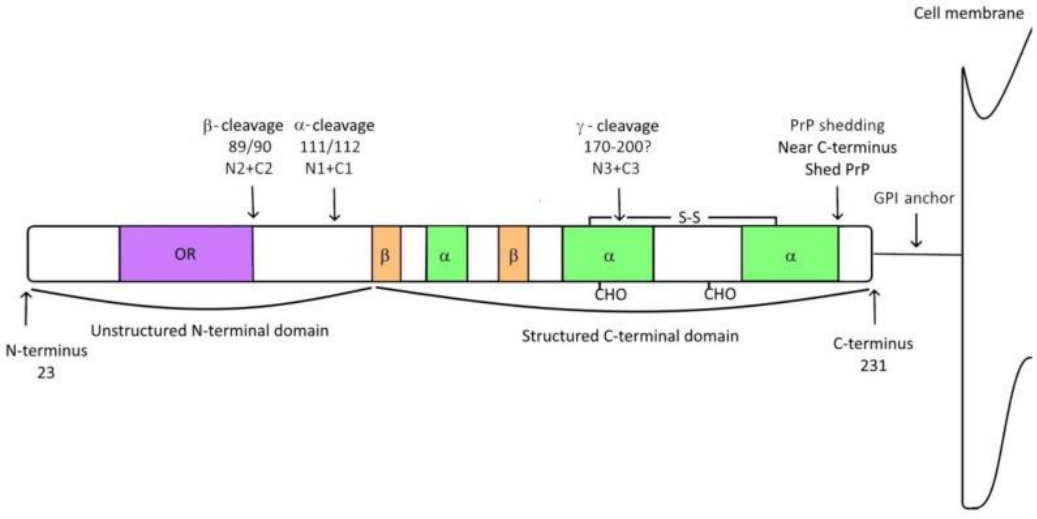

Figure 1: cleavage and shedding sites on the prion protein. (adapted from Kovač V, Čurin Šerbec V (2022)).

ADAM10 was found to be the sheddase that is responsible for the shedding of PrPC. The location at which the protein is removed from its anchor is Gly228/Arg229. The activity of ADAM10 is regulated by ADAM9 (Kovač V, Čurin Šerbec V (2022)). Shedding of PrPC is used as a regulatory mechanism, this is important for its involvement in toxic signalling cascades.

PrP^C is located at the cell membrane. To get to the cell membrane, the PrP^C is first moved from the Endoplasmic Reticulum (ER) through the Golgi apparatus to the cell surface, where it will actively signal (Chakrabarti O, et al (2009)). This expression is highly regulated, as PrP^C is only expressed in lipid rafts and can be ingested to control for the amount of PrP^C expressed. This expression of PrP^C mainly occurs in the central nervous system, although it can be found in other cell types as well (Castle AR, Gill AC (2017)).

PrP^C is expressed in neurons, astrocytes, oligodendrocytes, and microglia. It is found to work neuroprotective against Bax driven apoptotic signalling. Another functional aspect of PrP^C is its protection against oxidative stress. This may be possible due to the β - cleavage.

PrP^C is described to be involved in cell signalling, for example in neuritogenesis. Neuritogenesis is the process of forming, extending, and branching of neurites. It takes place in the development of the nervous system to form the complex neuronal networks. The membrane bound PrP^C can interact with other transmembrane proteins, one of them is the neural cell adhesion molecule (NCAM) (Santuccione A, et al (2005)). Interacting with NCAM causes PrP^C to signal for neuritogenesis via tyrosine kinase Fyn, this is mainly due to the N-terminal sequence of the PrP^C. Researchers have shown that a knockout of PrPC shows less Fyn activity and therefore less neuritogenesis. Fyn kinase activity is also associated with stress protection via calcium release from storage in the ER (Santuccione A, et al (2005)).

PrPC is also thought to be involved in the ER stress response. This is a reaction to accumulation of unfolded and misfolded protein in the ER. A natural response of the cell is to activate ERAD; ER associated degradation. This is a process in which the unfolded and misfolded proteins get labelled for degradation by proteases. The elements needed for this ER stress response are thought to be linked to PRNP promotor activity. However, there is no clear data supporting this claim (Castle AR, Gill AC (2017)).

The capability of PrPC to bind CU2+ is still a topic of debate. PrPC is shown to be capable of binding CU2+, but the relevance of this is still unknown. Binding of Cu2+ is shown to work against ROS, resulting in the promotion of β-cleavage. Which is thought to be neuroprotective, however this is only shown at levels of CU2+ far exceeding physiological levels normally found (Chattopadhyay M, et al (2005)).

Neurodegeneration in prion diseases

Prion diseases are characterised by neurodegeneration. The loss of neurons and neuronal function is seen in TSE as large vacuoles in the cortex and cerebellum (Takemura K, et al, (2004)). The spongiform degeneration can be diffuse or focal. The mechanism through which this vacuolation occurs is not known. It is thought that

abnormal autophagy or maybe the accumulation of PrP^{Sc} could be play a role (Soto C, et al (2011)). Neuroinflammation is another process that is linked to neurodegeneration. It can occur when microglia in the brain get activated to a primed state. In this primed state the microglia are ready to respond to pro-inflammatory signals. It is shown that treatment in mice with lipopolysaccharides during a prion infection resulted in rapid pro-inflammatory cytokine response. On top of this increased microglial activation, increased neurodegeneration and accelerated disease progression happened (Mabbott NA, et al (2020)).

Through which mechanism do misfolded prion protein cause neurodegeneration?

What causes prion misfolding?

In genetic prion diseases the cause of PrP^{C} misfolding lies in the PRNP gene. Most of these mutations have a very high penetrance, meaning that the percentage of people having clinical symptoms with a certain mutation is very high. These mutations are thought to alter the folding of the PrP^{C} at one of the α helices. One mutation mostly commonly associated with GSS is P102L. The amino acid proline at codon 102 is changed into a Leucine, resulting in a conformationally different protein. Some codons are associated with polymorphisms. And asparagine at codon 178 in combination with a methionine at codon 129 is associated with FFI. However, an asparagine at codon 178 in combination with a valine at codon 129 is then again associated with gCJD. Multiple mutations can be associated with a certain type of prion disease, for example E200K and V210I are also associated with gCJD. Most of these mutations are located in the globular domain of the C-terminal of PrP^{C}.

The polymorphisms in the PRNP gene can alter the risk of the disease, a good example is codon 129. Homozygosity for Valine or Methionine at this codon increases the chance of sCJD, and it lowers the age of onset in genetic CJD. In almost all tested cases of vCJD homozygosity for methionine was present.

Mutations also can occur in the octa repeated sequence of the N-terminal of PrP^{C}; however, the number of repeats is most contributing to clinical phenotypes. An insertion of one repeat is considered benign. More repeats inserted is associated with an earlier age of onset and a shorter duration of illness. Less than eight repeats present a more CJD-like phenotype, while more than eight repeats present a more GSS-like phenotype. Deletions of octa repeated sequences are also documented, however to a lesser

extend. Only a few cases of two octa repeated sequence deletions are documented, this is likely due to a very low penetrance. There is individual variation in the number of repeats and the presentation of clinical symptoms.

What are consequences of prion misfolding?

PrP^{C} can be converted into PrP^{Sc} at the membrane or within multivesicular bodies, most of the misfolding occurs at in the multivesicular bodies. When PrP^{C} is converted into PrP^{Sc} its structure changes from predominantly α-helices to a β-sheet rich structure. The exact mechanism through which this occurs is unknown. It is likely that fragments of the β-sheet of PrP^{Sc} can align with the amino acid sequence of PrP^{C} and will act as a steric zipper (Sigrudson CJ, et al (2019)). The complementary amino acids in the steric zipper bind PrP^{C} and form growing fibrils. It is shown that changes in the steric zipper are followed by a less functional alignment of PrP^{C} and PrP^{Sc}, blocking the conversion of prion proteins. These β-sheet rich structures can bind and form protein aggregates. These aggregates can disrupt the function of the cell.

Transmission and infectiousness of prions

Prion diseases that do not originate from a genetic mutation or spontaneous misfolding need to be acquired through the transmission of prions from one organism to the other. The most likely way to be infected with a prion disease is via oral intake. Following infection via oral route, the prions accumulate in the gut associated lymphoid tissue and start amplification (Gough KC, Maddison BC, (2010)). This lymphoid tissue connects to other parts of the lymphatic system, like lymph nodes and the spleen. These are connected to the enteric nervous system, which in turn allows the prions to spread to the CNS. From the CNS the prions can spread throughout the entire body as is seen in further progressed stages of the disease. There are differences between the species infected with prions. For example, oral BSE infection of cattle leads to minimal lymphatic involvement and a spread of prions mainly to the CNS. This same infectious agent does activate the lymphatic system in human vCJD, and sheep experimentally inoculated with prion of BSE origin. In similar manner the genotype of the PRNP gene also plays a role in the determination of infection in the lymphoid tissue. On top of that, prions are found to be spread through the blood. This is likely due to the presence of lymphoid cells in the vascular system, carrying the misfolded proteins (Gough KC, Maddison BC, (2010)).

Researchers have shown that the transmission of prions depends on the disease. Scrapie and CWD are examples of easily transmitted prion diseases. The presence of

PrP^{Sc} in excreta and secreta such as milk, placenta, and faeces has been taught to be a main source of disease transmission. Prion diseases such as BSE and sCJD do not transmit as easily. Prion causing BSE and sCJD are not present in excreta and secreta, and therefore not able to transmit as easily between individuals. However, BSE is very infectious via oral transmission in cattle (Gough KC, Maddison BC, (2010)).

What is the link between presence of misfolding prions and neurodegeneration?

One of the mechanisms PrP^{Sc} is thought to exerts its neurodegenerative function is via ER stress. PrP^{C} undergoes posttranslational changes in the ER, however not every protein is folded correctly. Misfolded proteins can aggregate and will build up within the Golgi apparatus or the endoplasmic reticulum. This buildup will cause ER stress and leads to the unfolded protein response (UPR). This is a response mechanism in which the cell shuts down its protein translation. One of the molecules that is phosphorylated as reaction to the UPR is eukaryotic translation initiation factor 2 subunit-α (eIF2α). The phosphorylation of eIF2α inhibits its function, resulting in an inhibition of protein synthesis throughout the cell. Further increasing eIF2α phosphorylation is shown to induce pathological mechanisms (Scheckel C, Aguzzi A (2018)).

PrP^{Sc} infection in the central nervous system is accompanied by extensive microglial and astrocyte activation (Gómez-Nicola D, et al (2013)). The microglia can be activated to produce proinflammatory cytokines, contributing to a chronic inflammatory phenotype (Li B, et al (2021)).

PrP^{C} shedding also plays a suspected role in the mechanism of prion disease, however this role is not fully understood yet. One theory is that shedding of PrP^{C} works protective against prion disease, since shedding removes PrP^{C} from the cell membrane. Thereby removing a possible ligand in the signalling pathway. Research has shown that artificially removing the PrP^{C} in a similar fashion as shedding resulted in a diminished formation of PrP^{Sc}. It should be noted that this artificial shedding is more efficient than shedding that occurs during normal processing of PrP^{C}. It should also be noted that regulating the ADAM10 mediated shedding did not alter the formation of PrP^{C} (Altmeppen HC, et al (2012)).

The other theory is that shedding of PrP^{C} might favour prion diseases. When the PrP^{Sc} is shed, it can spread more easily and induce misfolding in other prions. It is even shown that the removal of the GPI-anchor does not affect the formation of new PrP^{Sc}. In vivo research showed that normal expression levels of anchorless prions did lead to neurological symptoms similar to GSS. Mutations found in the PRNP gene of GSS

patients result in anchorless Prions, similar to the PrP^C shedding simulated in research (Altmeppen HC, et al (2012)).

Discussion

Prion diseases are complex diseases that are not fully understood. Misfolding and aggregation of proteins have shown to be detrimental for the normal function of the cell. This is not a process unique to prion diseases, there are more neurodegenerative diseases that acquire protein aggregates that disrupt cell function. Examples are Huntington's disease (HD) and Alzheimer's disease (AD). HD characterised by progressive motor symptoms, such as loss of voluntary movement, bradykinesia and rigidity, muscle atrophy, and cognitive deficits. These cognitive deficits start with slowness of processing, but progress into dementia. Psychiatric symptoms are also very common. Neurodegeneration of HD is seen as gradual atrophy of the striatum, however in later stages of the disease more regions of the brain can be affected (Gil JM, Rego AC (2008)). The protein that plays an important role in the disease mechanism is huntingtin. In its normal function it is taught to play an essential role in the embryonic development. In huntingtin a CAG repeat is found, normally containing up to 35 repeats. Patients with HD have 36 or more repeats, while more than 42 show full penetrance and full symptoms (Jimenez-Sanchez M, et al (2017)). Similar to Prion diseases, huntingtin forms β-sheet. These β-sheet bind together with hydrogen bonds and results in aggregates that accumulate in the cell, however it is still debated whether these protein aggregates contribute to toxicity in the cell. Another similarity to prion diseases is that protein degradation mechanisms are linked to HD. Studies have shown that the expression of extended huntingtin impairs proteasome activity, resulting in less degradation of pathological huntingtin. However, there are also reports that show protein degradation is not affected by the presence of elongated huntingtin. Another similarity between HD and prion diseases is reactive gliosis (Jimenez-Sanchez M, et al (2017)). Also, the presence of neuroinflammation is shared with HD and prion diseases.

Another example of a protein aggregating neurodegenerative disease is AD. It is characterised by progressive cognitive impairments, memory loss, and behavioural changes that impair daily function. Typical for AD is degeneration of the brain starting from the hippocampus in early stages of the disease. During disease progression the neurodegeneration will spread throughout the entire cortex in the later stages. One of the main pathological hallmarks of AD are amyloid bets plaques (Aβ) (Ramachandran AK, et al (2021)). In normal function amyloid precursor proteins (APP) is cleaved of by α, β, and γ secretases in a balanced manner. In AD this is imbalanced, β and γ secretases produce Aβ fragments that start aggregating together. These aggregations start accumulating and disrupting normal cell function, a similar process as aggregations of

PrP^{Sc} in pion diseases. Another protein aggregate that develops in AD are neurofibrillary tangles (NFTs) (Ramachandran AK, et al (2021)). Tau proteins bind microtubules to support neuronal structure. In AD, tau proteins are hyperphosphorylated. This hyperphosphorylation causes tau to bind less to microtubules, leading to changes in neuronal structure. The tau proteins start self-polymerising, forming NFTs. Another similarity shared with prion diseases is the microglia activated neuroinflammation. In AD, the presence of Aβ plaques causes the initiation of the neuroinflammatory response. Pro inflammatory cytokines signal for an adequate immune response, affecting all kinds of functions in neurons, leading to cell death (Thakur S, et al (2023)). Comparing AD and HD with prion diseases show many similarities in neurodegenerative mechanisms. The main similarity is the deposits of protein aggregations that disrupt cellular function. Also, can be appreciated that neuroinflammation in all three an important mechanism is that causes neurodegeneration.

Conclusion

Prion diseases are complex disorders involving the prion protein in its misfolded conformation. The normal function of the prion protein is still in some cases debated, like its function in Cu2+ binding. The main consensus is that PrPC is involved in the development of the CNS, via a process called neuritogenesis. Due to its function not being fully understood, the mechanisms through which misfolding of PrPC exerts its pathology are also not fully known. The involvement of genetic mutations in the PRNP gene is a mechanism that is better understood. The presence of homozygosity at codon 129 is an important risk factor in the development of sCJD, while in vCJD almost all cases tested were associated with heterozygosity. It is likely that the molecular mechanism of pathology is related to the cleaving and shedding of PrPC/Sc. Truncated parts of the Prion protein can play a role in ROS formation, activation of proinflammatory cell phenotypes and inducing of misfolding of PrPC. Misfolded PrPSc can aggregate by alignment of β-sheet rich regions in the amino acid chain and disrupt the function of the cell. The induction of ER stress mechanisms is thought to have a detrimental effect on the function of the cell. While a lot of evidence is showing the involvement of PrPSc in cellular mechanisms that result in neurodegeneration, the precise part is not yet understood. Fully elucidating the function of PrPC and PrPSc can be of importance in revealing all the pathways the protein is involved in. Allowing for a better understanding of pathological mechanisms that are at play in prion diseases.

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