**Prions and Prion Diseases**

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**Introduction**

Prions, by definition, are proteins that can cause normal proteins to misfold. Subsequently, these newly formed misfolded proteins cause some of the adjacent normal proteins to misfold in the same way. Therefore, it is said that prions ‘propagate’, or less accurately, ‘infect’ within our body. (The Johns Hopkins University et al., 2021)

To understand prion diseases, we need to know what prion proteins are. The production of prion proteins is no different from other proteins such as hemoglobin and myoglobin. Specific genes first cause a chain of amino acids with a specific sequence to be produced. This amino acid chain is then cleaved and folded in a specific way to form a three-dimensional structure. Prion proteins which have been folded normally and can be found in normal cells are cellular prion proteins (PrPc). In contrast, prion proteins which have not been folded abnormally, and should not be found in normal cells are scrapie prion proteins (PrPSc).

**Cellular prion proteins (PrPc)**

The function of PrPc is not fully known. However, studies in which cells are genetically modified to be able or unable to produce prion proteins (PrPc) have given us some directions to find out the answer to this question. In research which studied human neurons, Bax, a protein promoting apoptosis, a mode of cell death, was induced to be produced inside a foetal neuron in culture. In neurons that did not encode and express PrPc the apoptotic rate was nearly 90%. In contrast, in neurons where PrPc was encoded and expressed, the apoptotic rate dropped significantly to 10%. This implicates that PrPc may play a role in protecting neurons from undergoing apoptosis and dying. (Bounhar et al., 2001)

PrPc may be important in the peripheral nervous system, which includes the nerves stretching from the brain or the spinal cord. In a study, mice underwent genetic modification such that the gene encoding PrPc was knocked out. Mice which had undergone such experimental procedure were found to undergo demyelination in peripheral nervous system. This means, fat that encloses the nerve cells inside nerves, which is myelin, reduced. Without sufficient fat insulating the nerve cells from the outer aqueous environment, signals transmitting along them can be easily leak out. The result is that sensation or movement may be slowed down or even lost. (Bremer et al., 2010) A microscopic study revealed that the N-terminal region of the amino acid chain, i.e. the tail of PrPc, interacted with a specific G-protein coupled receptor called GPR126. Since GRP126 is responsible for receiving neuronal signals and initiating a cascade of activities to induce cellular changes, the experiment implicates that PrPc may help relay signals from nerve cell, participating in the control and homeostasis of the amount of myelin inside Schwann cells. (Küffer et al., 2016)

Being expressed in the nervous system, PrPc may be involved in other cognitive functions. When normal mice sleep, different sleeping stages progress and cycle through a specific duration of time. However, for mice that lack PrPc, sleep stages cycle faster. In addition, they experience more brief awakenings during sleep. (Sánchez-Alavez et al., 2007)

Other than these physiological functions, PrPc is also involved in metal ion homeostasis, immune system regulation, and mitochondrial homeostasis. However, the role that PrPc plays in these domains remains unclear. (Castle & Gill, 2017)

**Scrapie Prion Proteins (PrPSc)**

To fold an amino acid chain into a three-dimensional protein structure, the chain has to be arranged into alpha helixes, in which amino acid chain spirals, or in the form of beta sheets, in which amino acid chain presents like a pleated sheet. In cellular prion proteins (PrPc, the three-dimensional structure is built up primarily by alpha helixes, with beta-sheets constituting less than 5% of the structure. In contrast, in misfolded scrapie prion proteins (PrPSc), more than 50% of the three-dimensional structure is made up of beta-sheets which coil up like a solenoid. (Rufai et al., 2019)

In PrPSc, beta-solenoids exist with four rungs. It was suspected that the outermost rung of the PrPSc beta-solenoid, which are exposed to the outer environment, ‘stick’ to PrPc, and cause the normal PrPc to misfold into a new PrPSc. A protofilament is thus formed. Such propagation process occurs at the ends of two protofilaments simultaneously, causing them to intertwine with each other to form a double fibril. (Vázquez-Fernández, 2016) Forming around neurons, these prion fibrils segregate different nervous tissues and form spongelike holes in our central nervous system, disrupting neuronal signaling and causing symptoms such as dementia and behavioural changes. (Oregon Health & Science University Brain Institute, n.d.)

Diagram

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A: A PrPSc fibril, which consists of two protofilaments; B: A close-up of a PrPSc fibril showing the four rungs of a PrPSc.

*(Picture created by Vázquez-Fernández et al., cited from Vázquez-Fernández, 2016)*

It is unclear how PrPSc travels from our digestive system to the nervous system. Research points at Tunnelling nanotubules (TNT), which are cytoplasmic extensions that transiently bridge two cells. (Rufai et al., 2019) The fact that PrPSc is highly expressed in Peyer’s patches, which are aggregates of lymphatic cells right below the intestine epithelium, suggests that prion transmission involves the immune system. (Marshall et al., 2018) Therefore, it is suspected that TNT and immune cells are involved in the gut-brain transmission of PrPSc.

**Epidemiology of Prion Diseases**

Prion diseases were first identified among cattle as bovine spongiform encephalopathy (BSE). The name of this disease suggests its major characteristic – cattle’s’ encephalon, which means the brain, becomes pathologically spongelike. Since the disease manifests as behavioural changes and physical immobility, the disease also gains its nickname as ‘mad cow disease’. After humans consume the beef that originates from prion-infected cattle, they may develop variant Creutzfeldt-Jacob disease (vCJD).

In the 1980s and the early 1990s, a BSE outbreak occurred in the United Kingdom, in which thousands of cattle died due to the disease. However, lacking knowledge about BSE, humans continued to consume the beef from these cattle, being directly exposed to PrPSc. Recent studies estimated that one in 2000 people in the UK might carry PrPSc. (Callaway, 2013)



A cow which is allegedly suffering from BSE

*(Picture cited from a website of Centers for Disease Control and Prevention, U.S. Department of Health & Human Services)*

However, despite the high prevalence of PrPSc carrier, only 178 cases of vCJD is reported in the UK. (Gill et al., 2020) It should be noted that the development of vCJD is different among people. Scientists had analyzed the genes of patients of all clinical cases. In the gene that encodes cellular prion protein (PrPc), it was found that all patients were methionine homozygous at codon 129. This means, in a set of chromosome, if the genes, which are inherited from both your biological parents, are also responsible for encoding methionine at the 129th amino acid along the amino acid chain, you may be more susceptible to developing vCJD after being exposed to PrPSc. (Bougard et al., 2018) In contrast, if the genes inherited from one or both of your biological parents encode valine instead, vCJD is less likely to develop. This means that the vCJD onset risk is lower among people with ‘VM’ or ‘VV’ genes when compared with those with ‘MM’ genes.

Alarmingly, the first vCJD patient who had ‘VM’ genotype was reported in 2016. (Mok et al., 2019) This led to worries that people with ‘VM’ or ‘VV’ genes were in fact not ‘immune from’ vCJD, but only had very long incubation periods such that vCJD occurred several decades after their exposure to PrPSc. Given that PrPSc carriers are highly prevalent, and there is a large population with ‘VV’ or ‘VM’ genotype, it is reasonable that we are just at the start of the second wave of vCJD outbreak, and we may be seeing another hundred of vCJD cases in the near future.

However, we are totally not prepared to cope with the potential vCJD outbreak. Although research related to BME and vCJD was intense in late 1990s and early 2000s, it significantly slowed down in the recent decade. The society has seemingly arrived a consensus that prion diseases have been well contained, and another wave of outbreak is not likely to happen. Investors thus become much less motivated to push the academic field to initiate related research projects. Moreover, the transmission and propagation mechanism of PrPSc remain unclear, rendering scientists to be difficult to investigate the development of drugs. We are likely to be unable to treat vCJD patients in the potential wave of outbreak.

**Conclusion**

It is undoubted that both normal prions or misfolded prions are very unclear in terms of their function and mechanism of interaction. Without sufficient knowledge about prions, we are lacking suitable drugs and therapies to cope with prion diseases. However, prion diseases, in particular vCJD, may cause hundreds of deaths as PrPSc carriers are potentially facing an end in their incubation periods. The society should implement suitable protocols to cope with the potential outbreak and become more prepared to help potential vCJD patients.

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