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Introduction to Current Progress in Advanced Research on Prions

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Abstract

Prion diseases or transmissible spongiform encephalopathies (TSEs) are fatal neurological diseases that include Creutzfeldt–Jakob disease (CJD) in humans, scrapie in sheep and goats, bovine spongiform encephalopathy (BSE) in cattle, camel spongiform encephalopathy (CSE) in camels (Babelhadj *et al.*, 2018) and chronic wasting disease (CWD) in cervids. A key event in prion diseases is the conversion of the cellular, host-encoded prion protein (PrP^C) to its abnormal isoform (PrP^{Sc}) predominantly in the central nervous system of the infected host (Aguzzi *et al.*, 2004). These diseases are transmissible under some circumstances, but unlike other transmissible disorders, prion diseases can also be caused by mutations in the host gene. The mechanism of prion spread among sheep and goats that develop natural scrapie is unknown. CWD, transmissible mink encephalopathy (TME), BSE, feline spongiform encephalopathy (FSE), and exotic ungulate encephalopathy (EUE) are all thought to occur after the consumption of prion-infected material.

Most cases of human prion disease occur from unknown reasons, and > 20 mutations in the prion protein (PrP) gene may lead to inherited prion disease. In other instances, prion diseases are contracted by exposure to prion infectivity. These considerations raise the question of how a mere protein aggregate can bypass mucosal barriers, circumvent innate and adoptive immunity, and traverse the blood–brain barrier to give rise to brain disease. Here, we will briefly introduce a few topics in current prion studies.

Risk assessment in food safety and for blood products

The European Food Safety Authority (EFSA) has been requested several times over recent years to provide scientific advice in the area of animal TSEs [i.e. BSE, classical scrapie, atypical scrapie and chronic wasting disease (CWD) in ruminants]. In particular, there is a

requirement to perform a risk assessment and to address specific questions of the zoonotic potential of these prion agents. Advice has been sought on some occasions by the European Commission in order to provide updated information on the zoonotic potential of TSEs other than BSE.

In the past, EFSA and the former Scientific Steering Committee (SSC) of the European Commission were asked to reflect on the zoonotic potential of CWD and the possible role of cervids in the transmission of TSEs to humans. In 2003, the SSC concluded that a theoretical risk of prion transmission to humans consuming products of CWD-affected cervids of all ages in countries where CWD exists cannot be excluded. The SSC also concluded that the early and widespread involvement of tissues in CWD infected animals did not allow specified risk materials (SRM) to be defined. Neither was it possible to define a lower age cut-off for cattle in relation to BSE. In 2004, the EFSA concluded that even although human TSE-exposure risk through consumption of game from European cervids could be assumed to be either non-existent or minor, no final conclusion could be drawn due to the overall lack of scientific data (EFSA, 2004).

In recent years there have been several important developments in the scientific understanding of vCJD [EFSA Panel on Biological Hazards (BIOHAZ, 2011)], as outlined below:

- 1 A case report described a 30-year-old man who died in January 2009 with symptoms suggestive of vCJD. This individual had a genotype (heterozygote case) previously not associated with the disease. This created concern that there may be a second wave of vCJD cases in humans with a different genetic background.
- 2 The identification of a further possible vCJD infection in the spleen of a patient with haemophilia A in the UK raised the possibility that vCJD infection can be transmitted from person to person through the use of plasma-derived products.

Based on these developments, a number of questions were raised by the European Commission. Specifically, should the current assumption on the number of people who may develop vCJD in the future be reviewed? How does this impact on the current assumptions regarding transmissibility through blood transfusion and tissue/cells transplantation? Does this affect the number of individuals at risk of developing vCJD following a transfusion/transplantation? Are there measures that can be implemented to reduce the potential risk? The authors in this book will explain the current situation based on the latest scientific evidence.

Protein misfolding neurodegenerative diseases

Some research suggests that other proteins demonstrating prion-like behaviour play a role in other neurodegenerative diseases, including Alzheimer's, Parkinson's and Huntington's diseases, as well as amyotrophic lateral sclerosis (ALS) (Guo *et al.*, 2014). Recent work in humans suggest that A β can aggregate into structural variants with distinct pathological traits. By using extracted fibrils from the brains of patients with Alzheimer's disease (AD) to seed the aggregation of synthetic A β , it has been shown that A β assumes a single, dominant conformation of a given brain with structural heterogeneity among AD patients.

A prion-like mechanism has been proposed to explain the apparent proliferation of α -synuclein aggregates in the brains of Parkinson's disease patients. Whether prion-like

conformational templating occurs when α -synuclein aggregate strains are propagated *in vivo* or *in vitro* remains unclear.

Mutant forms of the Cu–Zn superoxide dismutase 1 (SOD1) gene are known to be associated with 10% of familial ALS cases. Some of these mutations are associated with a disease that progresses rapidly, resulting in death within 3 years, whereas others are associated with a relatively slow disease course, with the patient surviving for more than 20 years. One potential explanation for this variability in disease progression is that the SOD1 mutation exhibits prion strain-like properties that may affect their ability to propagate within the central nervous system.

Pecho-Vrieseling *et al.* (2014) suggest the protein that creates the aggregates found in Huntington's disease patients, mutant huntingtin (mHTT), may spread from cell to cell. These studies provide a valuable insight into what is currently understood about the role of protein aggregates and Huntington's disease.

Prion clearance

Progressive accumulation of PrP^{Sc} can occur only if conversion of PrP^C to PrP^{Sc} is faster than PrP^{Sc} clearance. Therefore, studying the clearance of prions is arguably as important as studying their generation. *Prnp*^{-/-} mice develop more or less normally yet cannot replicate prions, making them a perfect model to study the half-life of the prion. On inoculation, residual infectivity all but disappears within 4 days, indicating that prions, which are commonly regarded as the most robust pathogens yet described, can be cleared *in vivo* with astonishing efficiency and speed. The identification of molecules and cells involved in prion clearance will be of great importance in the development of therapeutics of prion diseases (Aguzzi *et al.*, 2012).

Nepriylisin is a metalloprotease that is known to degrade extracellular amyloid protein such as A β . However, mice lacking or overexpressing neprilysin show no changes in prion pathogenesis. Therefore, prion clearance may be affected by extracellular proteases other than neprilysin, or by different mechanisms altogether (Glatzel *et al.*, 2005). In organotypic cerebellar slices, the pharmacogenetic ablation of microglia led to a 15-fold increase in prion titres (Falsig *et al.*, 2008), suggesting that microglia are the primary effectors of prion clearance. But how do microglia identify prions as targets for destruction? Milk fat globule epidermal growth factor 8 (Mfge8), a bridging molecule mediating phagocytosis of apoptotic cells, may represent a crucial link. *Mfge8*^{-/-} mice showed accelerated prion pathogenesis, accompanied by reduced clearance of cerebral apoptotic bodies and increased PrP^{Sc} accumulation and prion titre (Kranich *et al.*, 2010), suggesting Mfge8-mediated prion clearance in prion-infected mouse brain. Interestingly, these changes were observed in the C57BL/6x129Sv but not in the C57BL/6 genetic background. Therefore, besides Mfge8, other molecules involved in the phagocytosis of apoptotic cells could have the potential to clear prions *in vivo*. These newly identified molecules involved in the pathogenesis in prion diseases need to be studied in more detail. Other molecules related to the pathogenesis of prion diseases will be discussed in a later section of this book.

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