Prion and neuroinflammation: Creutzfeldt-Jakob disease

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Introduction

· Transmissible spongiform encephalopathies are fatal neurodegenerative and infectious disorders affecting humans and animals. Creutzfeldt-jakob is the most common in humans and is caused by a prion.

· The prion is a cellular protein whose secondary structure is altered due to a mutation that turn it into a pathogenic protein. The prion can replicate itself and other prions so it has the capacity to infect other cellular proteins, and precisely, the conversion from cellular protein (PrP^C) to the prion protein (PrP^{Sc}) is the key to understand the pathogenesis in the TSEs.

· One of the consequences of CJD is the neurodegeneration, which implicate neuronal loss, and this is mainly caused by apoptosis. Because of that, it has been proposed that apoptotic cell death is related to the influence of cytokines, which are produced by activated astrocytes and microglia. Therefore, it will be a inflammation although this haven't been demonstrated yet.

Creutzfeldt-Jakob disease

· Creutzfeldt-Jakob disease (CJD) is a rapidly progressive neurodegenerative disorder belonging to the human prion diseases and it is characterized by the accumulation of prion protein or PrP^{Sc} in the brain, leading to subsequent neurodegeneration.

· The mechanisms by which the disease appears in a given individual are variable. However, they are classified into 3 major groups, so we can find three different subtypes of CJD with different incidences in the population:

-Sporadic (85%): The etiology of the disease is strange, so the reason why the mutation appears in the protein is still unknown.

-Familial (14%): The mutation which causes the disease could be hereditable.

-Iatrogenic (1%): The disease occurs after exposure to Infectious material to contaminate human body parts (like cornea, brains or blood) or bovine spongiform encephalopathy tainted products.

Replication and intracellular propagation

Prion: the agent strain

·Understanding the molecular basis of CJD pathogenesis is key to determining the reasons for the observed phenotypic variability of the disease. To start the neuroinvasion, the most important peculiarity of prions is their ability to reconfigure to other similar proteins to alter its operation and become pathogenic: two hypotheses known as "refolding" and "seeding" models attempt to explain prion propagation, and both hypotheses are based on the protein only model.

."Refolding" model: PrP^{Sc} binds PrP^C and this binding may be assisted by one or more chaperons. The conversion occurs at this moment, and transfer the information of PrP^{Sc} into PrP^C. This new PrP^{Sc} guide anothers PrP^C to transform into PrP^{Sc} .

-"Seeding" model: PrP^{Sc} is composed of misfolded PrP monomers. When this structure is formed, PrP^C can then be recruited starting an autocatalytic formation of PrP^{Sc}. Initiation as a pathogenic self-propagation conversion reaction may be induced by exposure to a "seed" of aggregated PrP following prion inoculation

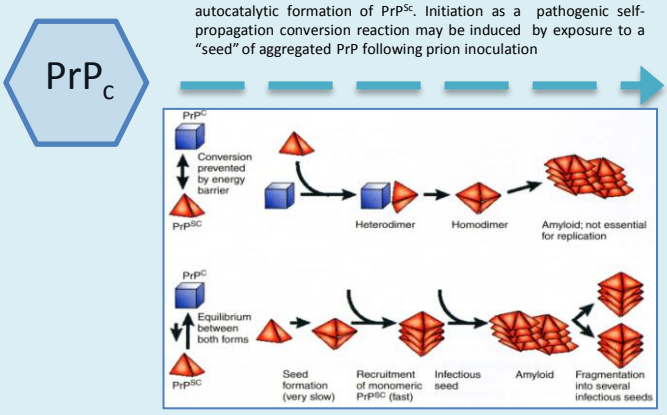

Figure 2: The *protein-only*hypothesis and the two models for the conformational conversion. Figure from (*Dickson et al. 2011)* [1]

Figure 1. The diagram resumes the entire process of the disease, from the cellular protein change her conformation into the prion to the death of the patient. The flashing arrows means a non demonstrate process. Figure modified from (*Eikelenboom et. al. 2002)* [2]

Course of the disease

Neurodegeneration in CJD

Various hypotheses have been proposed to explain the neurodegeneration, among them there are two principal theories:

· Neurotoxic effects caused directly by a region of the prion PrP^{Sc} (residues 106-126).

· Increased oxidative stress in neurons as a result of the gradual depletion of PrP^C protein, supposing that this protein has a molecular antioxidant function.

Neuroinflammation in CJD

There is still uncertainty regarding cytokine abnormalities in patients with CJD, because some reports suggest an increase in levels of the proinflammatory cytokines while others suggest an increase in levels of the anti-inflammatory cytokines , in CSF.

-In the one hand, there are some researches who indicate as a general rule that the diagnosis of CJD requires absence of classical inflammatory changes.

-In the other hand, microglia nevertheless up-regulate MHC class II molecules several hundredfold in this condition, so peripheral immune cells are absent but astrocytes produce proinflammatory factors. It means that could be an inflammatory response to the neurodegeneration.

What we know is that microglia is activated, but there is still a great deal to do: to clear up among a traditional point of view, when CJD was associated with a non-inflammatory disease, and the some recent research suggesting a partial inflammatory paper in human prion disease.

Conclusions

-There is still too much to investigate regarding prion disease, because there are some process about the infection and the disease's development that it's barely any information.

-The key in the neurodegeneration research is to define the role of PrP^C, because the only thing we know is that PrP^C are essential to balance neuronal transmission to the central nervous system, but we don't know what exactly do.

- We can find an interesting controversy about neuroinflammation, because we know that usually Creutzfeldt-Jakob is a non inflammatory disease, but microglia and astrocites are activated, so we can suspite about a neuroinflammatory process.

- Inflammatory response is tightly correlated with the progression of neurodegenerative disease: as soon as the theories abput neurodegeneration are clarified, we will find a solution to explain if there is a neuroinflammation in prion disease.

-To reduce neuroinflammation caused by prions could be a therapeutic target to try to minimize the damage at CNS.

References

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[3] Head, M. W., & Ironside, J. W. (2012). Review: Creutzfeldt–Jakob disease: prion protein type, disease phenotype and agent strain. Neuropathology and applied neurobiology, 38(4), 296-310.