

"A Prion"

A prion is an infectious agent thought to be the cause of the transmissible spongiform encephalopathy (TSEs). It is composed of entirely of protein material called *prp* (short of prion protein) that can fold in multiple structurally distinct ways. The word prion coined in 1982 by Stanley B. Prusiner derived from the words protein and infection, hence prion is short for "proteinaceous infectious particle".

Diseases caused by prions:

Sheep and goat ———> Scrapie

Cattle ———> Bovine Spongiform encephalopathy BSE, Mad cow disease

Human ———> Creutzfeldt Jakob disease (CJD)

Gerstmann Straussler Scheinker syndrome (GSS)

Fatal Familial Insomnia (FFI)

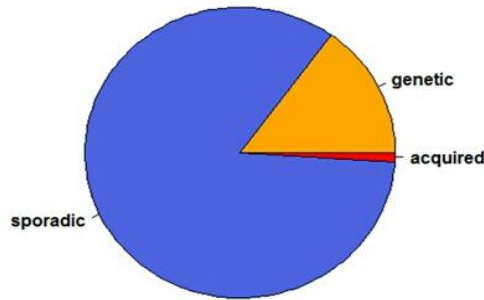
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Structure:

The protein that prions are made of (*prp*) is found throughout the body, even in healthy people and animals; however *prp* has a different structure and is resistant to protease. The normal form of the protein is called *prp^c* while the infectious form is called *prp^{sc}*. The C refers to cellular *prp*, it is a normal protein found on the membranes of cells, it has 209 amino acids in human, one disulfide bond and mainly alpha-helical structure, while the SC refers to scrapie, the protein typical prion disease occurring in sheep. It has a higher proportion of B-sheet structure in place of the normal alpha-helix structure; aggregation of these abnormal iso-forms forms highly structured amyloid fibers which accumulate to form plaques.

Transmission:

It has been recognized that prion disease can arise in three different ways: acquired, familial or sporadic. *Acquired* CJD results from exposure to an external source of abnormal prion protein. These sources estimated to be either medical procedures involving instruments used in neuron surgery and growth hormone from human sources of certain transplanted human tissues or from meat or other products from cattle infected with bovine spongiform encephalopathy "Mad Cow Disease" also grafts of Dura mater taken from patients with inherited CJD. *Familial* CJD is a hereditary form caused by certain changes in the prion protein gene; these genetic changes are "dominant". *Sporadic* CJD develops spontaneously for no known reasons, on average sporadic CJD first appears between age 60-65y.

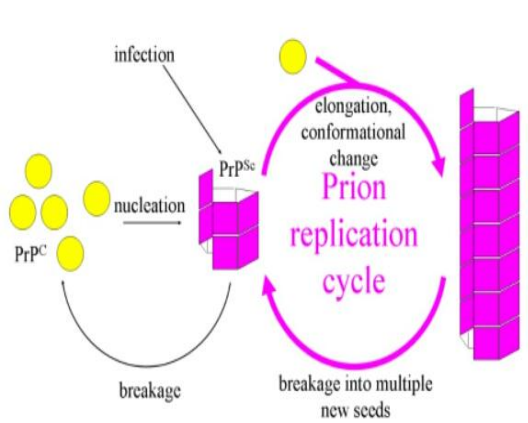


It is often assumed that the disease form directly interacts with the normal form to make it rearrange its structure. One idea the "protein x" hypothesis enables the conversion of prp^c to prp^{sc} into complex structure.

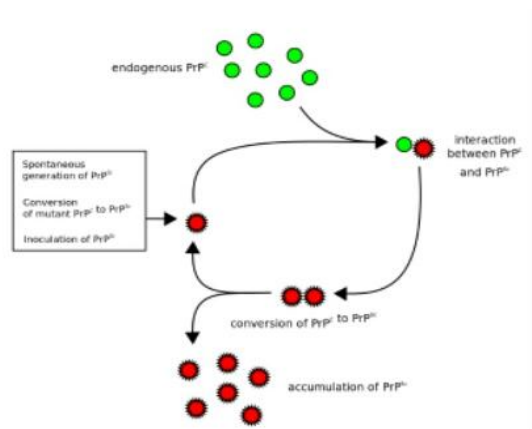
Prion Replication Mechanism:

Two hypothesis that tried to explain how prions replicate, the first one was **the heterodimer model**. This model assumed that a single prp^{sc} molecule binds to a single prp^c molecule and catalyzes its conversion into prp^{sc} . However a model of prion replication must explain both how prions propagate and why their spontaneous appearance is so rare.

An alternative model assume that prp^{sc} exists only as fibrils and that fibril ends bind prp^c and convert it into prp^{sc} then the quantity of prions would increase linearly forming ever longer fibrils.



An alternative model



Heterodimer model

Symptoms:

Specific Creutzfeldt Jakob disease symptoms experienced by an individual and the order in which they appear can differ significantly. Some common symptoms include:

- Depression
- Agitation, apathy and mood swings
- Rapidly worsening confusion, disorientation and problems with memory, thinking, planning and judgment
- Difficulty walking
- Muscle stiffness, twitches and involuntary jerky movements.

Diagnosis:

Rapid symptoms prognosis is one of the most important clues that a person may have Creutzfeldt Jakob disease. There is no tests that can conclusively diagnose sporadic CJD in a living person but the following tests may help determine whether an individual has CJD:

- Electroencephalogram (EEG)
- Brain magnetic resonance imaging (MRI)
- Lumbar puncture (spinal tap).

Medical Care:

- + Discontinue any medication that could impair or cause confusion
- + The transmissible spongiform encephalopathy are rapidly progressive neurodegenerative disease and fatal. No treatment has proven efficacious. Chemotherapy approach have focused on blocking the conversion of prp^c to prp^{sc}
- + Promising therapeutic approaches aimed to block the production of prp^{sc} are based on prp RNA interference, passive or active immunization as well as inhibition of prp^{sc} formation.