Prions — Definition, Structure, and Sterilization

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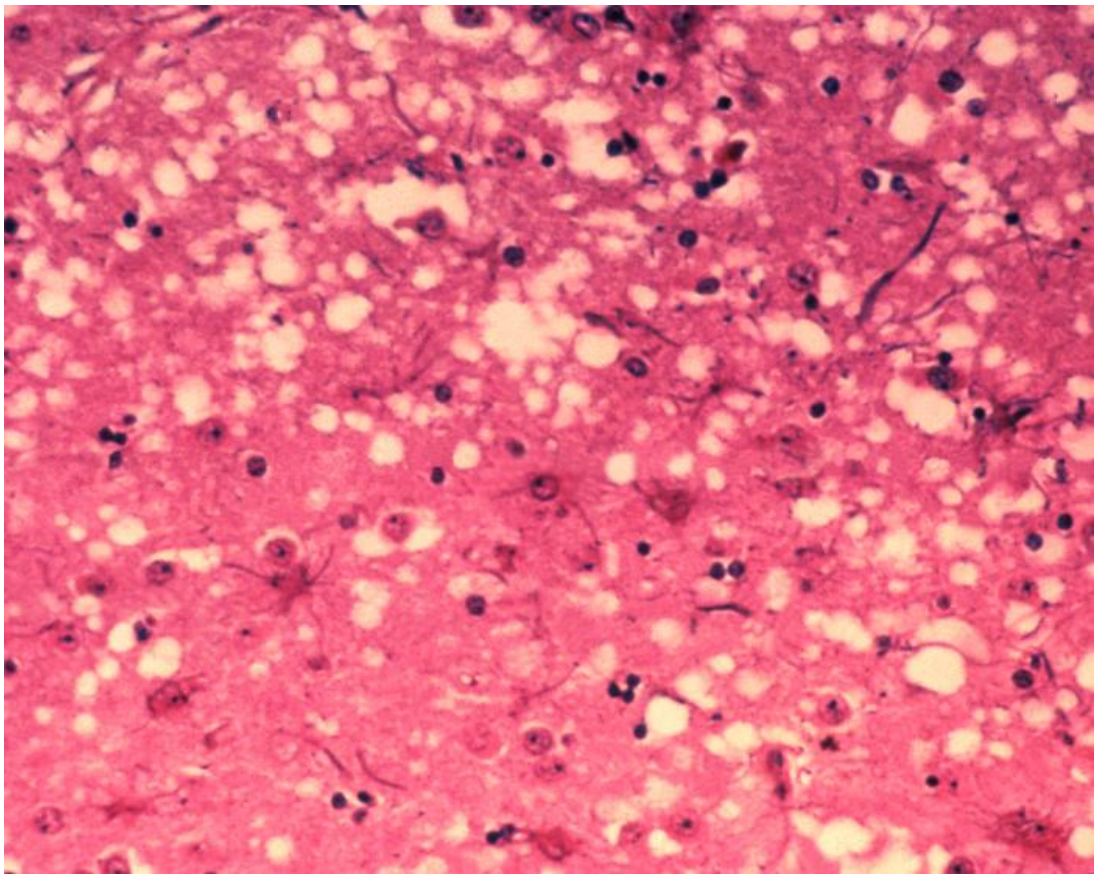
Prion is a proteinaceous infectious agent that causes fatal degenerative disease of nerves. Prions can be genetic, infectious or sporadic disease. The protein is able to structurally transform a normal occurring protein into an abnormal structural protein that is transmissible to other prion proteins. They are the main cause of transmissible spongiform encephalopathies.



Overview

Prions cause bovine spongiform encephalopathy in cows, commonly referred to as mad cow disease, and scrapie in sheep. Prions are also suspected to cause chronic wasting disease in deer.

In humans, prions can cause Creutzfeldt-Jakob disease, fatal familial insomnia, kuru, and Gerstmann-Sträussler-Scheinker syndrome. Multiple system atrophy is caused by misfolded alpha-synuclein, which is also classified as a prion disease.

When prions affect a healthy individual, they cause properly folded proteins to convert

into an amyloid form (aggregated beta-pleated sheets). When these sheets accumulate in abnormal quantities, they have the potential to damage the brain.

The structure of the prion protein is remarkably stable, and prions are resistant to denaturation. Thus, it is difficult to dispose of the infectious material.

Incubation Period of Prion Proteins

The incubation period can be determined by the rate at which the prion proteins replicate. The propagation depends on whether the animal possesses a normal prion protein or not. Animals that do not have the normal prion protein cannot develop or transfer the disease to others.

Discovery of Prion Proteins

Two London based researchers, Tikvah Alper and John Stanley Griffith, hypothesized that some transmissible spongiform encephalopathies are only caused by proteins. They also suggested that the agent causing spongiform encephalopathies and Creutzfeldt-Jakob disease was not affected by radiation because the particle was too small to be hit by ionizing radiation.

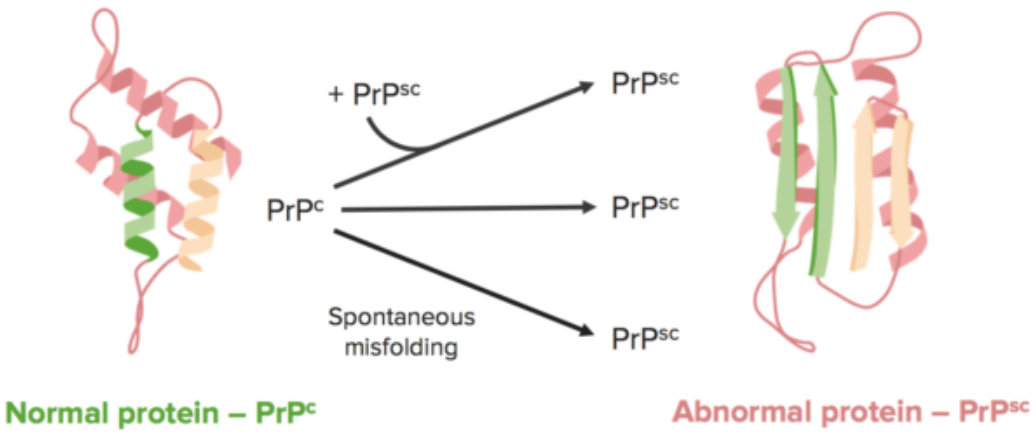
Later in 1982, Stanley B. Prusiner and his team managed to isolate the protein after 2 years of research. They discovered that the infectious agent was purely a protein. They also stated that the prion protein could occur in both normal and infectious forms.

Structure of Prion Proteins

Prion proteins are present throughout the body in humans and animals. The prion protein found in infections has a different structure and is **resistant to proteases**. Entry to the brain occurs through infection, resulting in the progressive breakdown of neurons and causing prion disease. All prion proteins are not infectious. The following are the different forms of prion proteins:

PrPc

This is a normal constituent of the cell membrane and has an alpha-helical structure. Normal prion proteins have important functions, which include cell-to-cell adhesion and communication in the brain. PrPc binds to copper ions with great affinity.



PrPres

This is an isoform of PrPc that is resistant to proteinase K and is structurally misfolded. It may or may not be infectious.

PrPSc

This is a structurally altered form of the normal PrPc which is always infectious and causes disease. It is a component of the infectious prion particles. The exact structure of the protein is still unknown but it has beta-pleated sheets that form amyloid fibers, which eventually accumulate and form plaques.

Function of Prion Proteins

The exact function of prion proteins is still being researched but experimental studies in mice have demonstrated that they play a role in the regeneration of myelinated nerve fibers. It has been shown that the breakdown of prion proteins causes the activation of myelin repair, and if this repair is hindered, then nerve demyelination occurs.

In studies conducted between 2004 and 2005, it was hypothesized that prion proteins play a role in the maintenance of long-term memory. In 2006, an article from the Biomedical Research Institute of Whitehead showed that prion proteins are necessary for the self-renewal of bone marrow. It stated that the expression of prion proteins on stem cells is necessary for self-renewal.

Mechanism of Prion Replication

The heterodimer model was the first to explain how prions replicate. This model stated that when a single molecule of PrPSc comes in contact with a molecule of PrPc, it catalyzes the conversion of the normal protein into the altered form, and this process continues until many defective protein molecules are formed.

Another model explains that PrPSc exists only in the fibril form and this fibril form binds to the normal PrPc causing its conversion into abnormal protein.

There should be a hypothesis that explains the exponential growth and replication that is observed during the disease process. This can be explained by a mathematical solution which states that exponential growth is the result of fibril growth and breakage. The exponential growth is determined by the square root of the PrPc concentration.

The process of prion replication has many implications in the design of drugs. A drug that will decrease the exponential growth will decrease the progression of the disease.

Diseases Caused by Prions

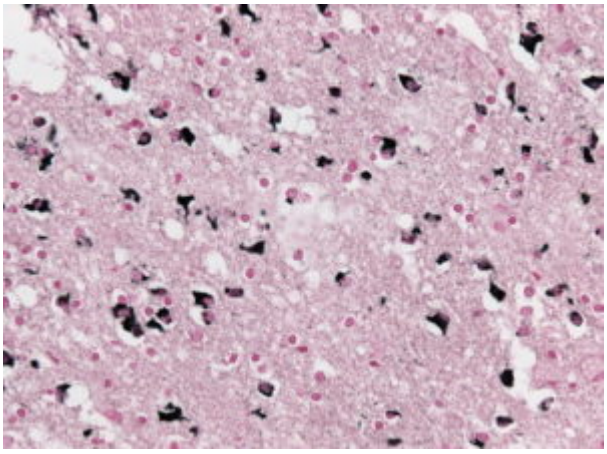


Image: Histology specimen displaying Papp-Lantos inclusions in the cingulate gyrus in a case of multiple system atrophy: Gallyas silver stain, ×200 magnification. By Jensflorian. License: CC BY-SA 3.0

- **Sheep**: scrapie
- **Cattle**: bovine spongiform encephalopathy
- **Mink:** transmissible mink encephalopathy
- **White-tailed deer:** chronic wasting disease
- **Cat:** feline spongiform encephalopathy
- **Ayala, oryx, greater kudu**: exotic ungulate encephalopathy
- **Ostrich**: spongiform encephalopathy
- **Humans:** iatrogenic and variant Creutzfeldt-Jakob disease, Gerstmann-Sträussler-Scheinker syndrome, fatal familial insomnia, Kuru, familial spongiform encephalopathy, multiple system atrophy
    - Diseases are sporadic, genetic, or acquired in origin
    - The abnormal prion proteins mimic an infectious agent that can cause transmission of disease to humans or that can be inherited as a mutant.

Sterilization

Generally, prions are resistant to heat, ionizing radiation, formaldehyde, and proteases. However, the aforementioned may reduce their infectivity. Decontamination relies on hydrolysis which destroys the protein structure. This can be done using sodium hydroxide, sodium hypochlorite, and acidic detergents like LpH. Autoclaving at 134°C for 18 minutes is considered effective.

The World Health Organization (WHO) has approved three ways to disinfect all heat-resistant instruments as follows:

- Immerse the instrument in 1N sodium hydroxide and place it in a gravity displacement autoclave for 30 minutes at 121°C. Thereafter, take the instrument out, rinse with normal water, clean, and repeat the routine sterilization process.
- Immerse in 1N sodium hypochlorite for 1 hour, rinse with water, place in a gravity displacement autoclave at 121°C for 1 hour.
- Immerse the instrument in sodium hydroxide or sodium hypochlorite for 1 hour, rinse with water, then transfer to a gravity displacement autoclave (121°C) or a porous load (134°C) for 1 hour, clean, and perform the routine sterilization procedures.

Potential Treatments and Diagnosis

There are no definitive means for diagnosing and treating prion disease but some methods are being used. These include:

- **Antibodies against PrP** have shown some promising effects. Antibodies against PrP were used in prion-infected mice and they were treated successfully under specific conditions.
- **Gene silencing** is another method still under trial in which the genes causing prion disease are turned off.
- **Stem cell therapy** is another proposed therapy for the treatment of prion diseases. It can be used to make new brain cells to replace the damaged brain cells.
- **Astemizole** is found to have an anti-prion activity that can cross the blood-brain barrier and inhibit the activity of prions.

References

Prion Diseases via cdc.gov

Atarashi R; et al. (Feb 2011): Ultrasensitive human prion detection in cerebrospinal fluid by real-time quaking-induced conversion

Saborio GP, Permanne B, Soto C (2001): Sensitive detection of pathological prion protein by cyclic amplification of protein misfolding

Notes