# Prions

**Prions** are misfolded proteins which characterize several fatal neurodegenerative diseases in humans and many other animals.It is not known what causes the normal protein to misfold; the abnormal three-dimensional Dr. Stanley Prusiner coined the term "prion" in 1982, which he defined as a small infectious pathogen containing protein but apparently lacking nucleic acid. The prion protein (PrP) is the critical component of these agents and may, in fact, be its exclusive constituent..Its,structure is suspected of conferring infectious properties. The word *prion* derives from "proteinaceous infectious particle"

Prions composed of the prion protein (PrP) are hypothesized as the cause of transmissible spongiform encephalopathies (TSEs),including scrapie in sheep, chronic wasting disease (CWD) in deer, bovine spongiform encephalopathy (BSE) in cattle (commonly known as "mad cow disease"), and Creutzfeldt-Jakob disease (CJD) in human.

In human, prions are believed to be the cause of Creutzfeldt–Jakob disease (CJD), its variant (vCJD), Gerstmann–Sträussler–Scheinker syndrome, fatal familial insomnia and kuru. All known prion diseases in mammals affect the structure of the brain or other neural tissue; all are progressive, have no known effective treatment and are always fatal. A prion disease is a proteopathy, other proteopathies include multiple system atrophy (MSA), a rare human neurodegenerative disease, features a misfolded version of a protein called alpha-synuclein.There is also evidence suggesting prions may play a part in the process of Alzheimer's disease and Parkinson's disease.



Discovering the mechanism of replication of prions has been a very difficult task. To find out how can a protein multiply without any cellular machinery was next to impossible. But this is what prions do. There are many other concepts related to prions that are unclear. Researches are being carried out to figure out the in and outs of prions for detailed studies.

### Structure

The protein that prions are made of (PrP) is found throughout the body, even in healthy people and animals. However, PrP found in infectious material has a different structure and is resistant to proteases, the enzymes in the body that can normally break down proteins. The normal form of the protein is called **$PrP^{C}$**, while the infectious form is called **$PrP^{Sc}$** – the *C* refers to 'cellular' PrP, while the *Sc* refers to

'scrapie', the prototypic prion disease, occurring in sheep.While **$PrP^{C}$** is structurally well-defined, **$PrP^{Sc}$** is certainly polydisperse and defined at a relatively poor level. PrP can be induced to fold into other more-or-less well-defined isoforms in vitro, and their relationship to the form(s) that are pathogenic in vivo is not yet clear.

### $PrP^{C}$

$PrP^{C}$ is a normal protein found on the membranes of cells. It has 209 amino acids (in humans), one disulfide bond, a molecular mass of 35–36 kDa and a mainly alpha-helicalstructure. Several topological forms exist; one cell surface form anchored via glycolipid and two transmembrane forms.The normal protein is not sedimentable; meaning that it cannot be separated by centrifuging techniques.

### $PrP^{res}$

Protease-resistant $PrP^{Sc}$-like protein ($PrP^{res}$) is an isoform of $PrP^{c}$ which is structurally altered and converted into a misfolded proteinase K-resistant form *in vitro*. To model conversion of $PrP^{C}$ to $PrP^{Sc}$ in vitro, Saborio *et al.* rapidly converted $PrP^{C}$ into a $PrP^{res}$ by a procedure involving cyclic amplification of protein misfolding.It has been made to distinguish between $PrP^{Sc}$, which is isolated from infectious tissue and associated with the transmissible spongiform encephalopathy agent



### $PrP^{Sc}$

The infectious isoform of PrP, known as $PrP^{Sc}$, is able to convert normal $PrP^{C}$ proteins into the infectious isoform by changing their conformation, or shape; this, in turn, alters the way the proteins interconnect. $PrP^{Sc}$ always causes prion disease. Although the exact 3D structure of $PrP^{Sc}$ is not known, it has a higher proportion of β-sheet structure in place of the normal α-helix structure

## Function

The physiological function of the prion protein remains poorly understood. While data from in vitro experiments suggest many dissimilar roles, studies on PrP knockout mice have provided

only limited information because these animals exhibit only minor abnormalities. In research done in mice, it was found that the cleavage of PrP proteins in peripheral nerves causes the activation of myelin repair in Schwann cells and that the lack of PrP proteins caused demyelination in those cells.

### PrP and regulated cell death

MAVS, RIPI, and RIP3 are prion-like proteins found in other parts of the body. They also polymerise into filamentous amyloid fibers which initiate regulated cell death in the case of a viral infection to prevent the spread of virions to other, surrounding cells.

### PrP and long-term memory

A review of evidence in 2005 suggested that PrP may have a normal function in maintenance of long-term memory.As well, a 2004 study found that mice lacking genes for normal cellular PrP protein show altered hippocampal long-term potentiation. A recent study that might explain why this is found that neuronal protein CPEB has a similar genetic sequence to yeast prion proteins. The prion-like formation of CPEB is essential for maintaining long-term synaptic changes associated with long term memory formation.



### PrP and stem cell renewal

A 2006 article from the Whitehead Institute for Biomedical Research indicates that PrP expression on stem cells is necessary for an organism's self-renewal of bone marrow. The study showed that all long-term hematopoietic stem cells express PrP on their cell membrane and that hematopoietic tissues with PrP-null stem cells exhibit increased sensitivity to cell depletion.

**Diseases caused by prions**

| Affected animal(s) | Disease |
|---|---|
| Sheep, Goat | Scrapie |
| Cattle | Bovine spongiform encephalopathy (BSE), mad cow |

| | |
|---|---|
| | disease |
| Camel | Camel spongiform encephalopathy (CSE) |
| Mink | Transmissible mink encephalopathy (TME) |
| White-tailed deer, elk, mule deer, moose[55] | Chronic wasting disease (CWD) |
| Cat[55] | Feline spongiform encephalopathy (FSE) |
| Nyala, Oryx, Greater Kudu[55] | Exotic ungulate encephalopathy (EUE) |
| Ostrich | Spongiform encephalopathy |
| Human | Creutzfeldt–Jakob disease (CJD) |
| | Iatrogenic Creutzfeldt–Jakob disease (iCJD) |
| | Variant Creutzfeldt–Jakob disease (vCJD) |
| | Familial Creutzfeldt–Jakob disease (fCJD) |
| | Sporadic Creutzfeldt–Jakob disease (sCJD) |
| | Gerstmann–Sträussler–Scheinker syndrome (GSS) |

| | |
|---|---|
| | Fatal familial insomnia (FFI) |
| | Kuru |
| | Familial spongiform encephalopathy |

## Types of Prion Diseases

Prion diseases can be of three types- acquired, sporadic, or genetic.

### Acquired Prion Disease

The acquired prion diseases occur when a person is exposed to the infectious protein. Though scary, these prions are rarely caught by the people. For eg., in kuru diseases, the prions were transmitted to people by cannibalism. Its main source was New Guinea pig.



### Genetic Prion Disease

The familial prion diseases are caused as a result of genetic transmissions. However, it is not necessarily inherited from the ancestors. It may be caused due to the mutation in some DNA.

### Sporadic Prion Disease

Prion diseases are also believed to be sporadic. This means that its cause is not confirmed. This form of prion disease is most common to date.

## Causes of Prion Diseases

The main cause of prion diseases is the abnormal folding and clumping of prions in the brain causing brain damage. This leads to memory impairment, changes in the personality, difficulties in moving.

Prions are by far the most dangerous infections caused by the agents already present within the body and are usually fatal. However, a lot has not been discovered about prion diseases.

## Risk Factors Involved

People with genetic history related to prion disease are at risk of Prion disease.

Eating meat infected by “mad cow disease” increases the risk of Prion disease.

Contaminated medical equipment or contaminated corneas can cause Prion disease.

## Symptoms of Prion Disease

Following are the symptoms of Prion diseases:

- Developing dementia
- Hallucinations
- Fatigue
- Stiffening of muscles
- Confusion
- Difficulty in speaking



## Transmission

It has been recognized that prion diseases can arise in three different ways: acquired, familial, or sporadic.It is often assumed that the diseased form directly interacts with the normal form to make it rearrange its structure. One idea, the "Protein X" hypothesis, is that an as-yet unidentified cellular protein (Protein X) enables the conversion of $PrP^{C}$ to $PrP^{Sc}$by bringing a molecule of each of the two together into a complex.

Current research suggests that the primary method of infection in animals is through ingestion. It is thought that prions may be deposited in the environment through the remains of dead animals and via urine, saliva, and other body fluids. They may then linger in the soil by binding to clay and other minerals.

A University of California research team, led by Nobel Prize winner Stanley Prusiner, has provided evidence for the theory that infection can occur from prions in manure.And, since manure is present in many areas surrounding water reservoirs, as well as used on many crop

fields, it raises the possibility of widespread transmission. It was reported in January 2011 that researchers had discovered prions spreading through airborne transmission on aerosol particles

## Sterilization

The World Health Organization recommends any of the following three procedures for the sterilization of all heat-resistant surgical instruments to ensure that they are not contaminated with prions

1. Immerse in 1N sodium hydroxide and place in a gravity-displacement autoclave at 121 °C for 30 minutes; clean; rinse in water; and then perform routine sterilization processes.
2. Immerse in 1N sodium hypochlorite (20,000 parts per million available chlorine) for 1 hour; transfer instruments to water; heat in a gravity-displacement autoclave at 121 °C for 1 hour; clean; and then perform routine sterilization processes.
3. Immerse in 1N sodium hydroxide or sodium hypochlorite (20,000 parts per million available chlorine) for 1 hour; remove and rinse in water, then transfer to an open pan and heat in a gravity-displacement (121 °C) or in a porous-load (134 °C) autoclave for 1 hour; clean; and then perform routine sterilization processes.