


PRIONS

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Introduction

- ❖ The word itself derives from (acronym of) ‘proteinaceous infectious particle’; meaning that the infectious agent consists only of protein with no nucleic acid genome.
 - ❖ Prions are the only known example of infectious pathogens that are devoid of nucleic acid.
 - ❖ The prototype of the prion diseases, scrapie, was first described after the importation of Merino sheep from Spain into England in the 15th century.
 - ❖ The name reflects the characteristic scratching behavior of diseased animals.
 - ❖ Scrapie is endemic in sheep in all countries except Australia and New Zealand.
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Introduction

- Bovine spongiform encephalopathy was first detected in 1986 in the United Kingdom.
- Epidemiological observations suggest that the cattle disease originated in the early 1980s when scrapie prions underwent a "species jump" and became established in cattle; rendered meat-and-bone meal produced from sheep carcasses and offal and fed to cattle is considered the probable source.
- In 1997, for his discovery of the bizarre nature of prions and their exceptional pathogenetic pathways, Stanley Prusiner was awarded the Nobel Prize in Medicine.



Introduction

- In 1963, **William Hadlow**, a veterinarian working at the Rocky Mountain Laboratory in Montana, United States, **proposed that the human disease kuru was similar to scrapie in sheep** and that it might be transmissible.
- Kuru, a fatal neurological disease, occurred only in the Fore tribe in the New Guinea highlands where ritualistic cannibalism was practiced on deceased relatives.
- Hadlow's idea led to the discovery by **Carleton Gajdusek** that kuru could be transmitted to chimpanzees, causing a disease indistinguishable from the human counterpart.
- For this discovery Gajdusek was awarded the Nobel Prize in Medicine.

Properties of Prions

- ❖ Prions have not been classified like viruses. There are no families, genera, or species. They first are identified by their host species and disease association.
- ❖ Then, they are characterized by their molecular and biological properties.
- ❖ Their primary amino acid sequence mainly reflects the host from which they were isolated. Certain biological properties are used to distinguish strains of prions, particularly scrapie strains.
 1. Incubation period and mortality pattern
 2. Distribution and extent of spongiform lesions and prion protein (PrP) plaques in brains (assayed by immunohistochemistry using labeled anti-PrP antibodies)
 3. Titer of infectivity in brains. Prion strains "breed true," giving reproducible results in this kind of biological assay system.



Properties of Prions

- Prions are normal cellular proteins that have **undergone conformational change** as a result of posttranslational processing of a normal cellular protein and thereby have become pathogenic.
- The normal protein, called **PrPc** (term for the normal cellular isoform of the prion protein), is composed of about **208 amino acids (Mr 27,000- 30,000)**.
- It is encoded in the genome of most mammals and is expressed in many tissues, especially in neurons and lymphoreticular cells.
- The **function of PrPc is unclear**; it has been found to bind copper, but knockout mice lacking the gene for the protein appear normal.

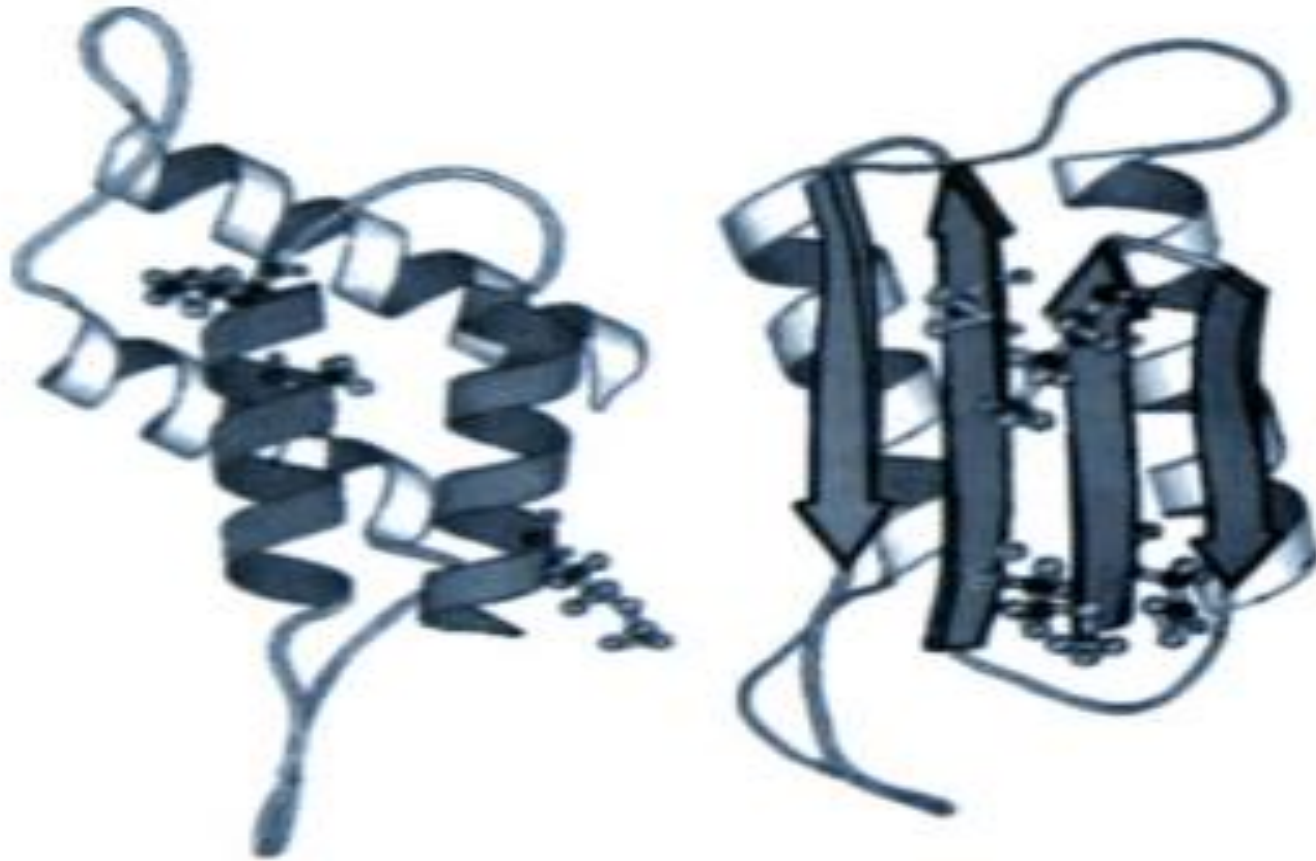


Properties of Prions

- The amino acid sequence of PrP_c and the **abnormal isoform of the protein, called PrP_{sc}** (term derived from the scrapie isoform of the prion protein, but in general use for all prion diseases), in a given host are identical.
- Only the conformation of PrP_{sc} is changed, from a structure made up predominantly of **α helices to one made up predominantly β sheets**.
- When a given animal prion is passaged in mice or hamsters the amino acid sequence of the recipient PrP_{sc} is that of the PrP_c of the recipient, not the donor.



FIGURE 40.1.



Structure of normal prion protein (PrP^C, the normal isoform of PrP protein) with prominent α helices (left) and PrP^{Sc} (the abnormal isoform) with prominent β sheets (right). [From F. Cohen, Structural clues to prion replication. *Science* **273**, 184–189 (1996).]

Properties of Prions

- In a particular host, there may be many different mutations in the PrP gene, each resulting in a slightly different PrP^{sc} conformation, each resulting in a different lesion pattern and different incubation and mortality pattern.
- This is the basis for the different prion strains.
- PrP^{sc} protein is very resistant to many environmental insults, chemicals, and physical conditions that would destroy any virus or microorganism
- PrP^{sc} is also resistant to endogenous proteases, which is the key to its accumulation into aggregates, called **scrapie associated fibrils** (SAF; term derived from scrapie but in general use for all prion diseases), that form neuronal plaques and cause spongiform damage and neuronal dysfunction.

Properties of Prions

Other notable characteristics of prions include:

1. They can reach very high titers in the brains of their hosts~laboratory strains passaged in hamsters can reach titers of $10^{11}\text{ID}_{50}/\text{g}$ of brain
2. As measured by ultrafiltration their size seems to be about 30nm
3. They are very resistant to UV- and γ -irradiation, having a very small radiation target size and also resistant to endogenous proteases.
4. They polymerize, forming helically wound filamentous rods 4-6nm in diameter, called SAF, which are visible by electron microscopy and which make up the plaques seen in neurons
5. They evoke no inflammatory or immune response in their host.

Diseases of Prions

DISEASE	HOST	SOURCE OF INFECTION
Scrapie	Sheep, goats	Not certain, possibly scrapie prion contained in feed, but more likely by direct contact and contamination of pastures by placentas and fetal tissues
Bovine spongiform encephalopathy	Cattle	Bovine spongiform encephalopathy prion contamination of meat-and-bone meal; some vertical transmission from cow to calf
Transmissible mink encephalopathy	Mink	Scrapie prion contamination of sheep carcasses and offal fed to mink
Chronic wasting disease	Mule deer, elk	Unknown in feral animals, possibly scrapie prion contamination of feed or contamination of paddocks in captive animals
Feline spongiform encephalopathy	Cats, felids in zoos	Bovine spongiform encephalopathy prion contamination of meat fed to animals
Exotic ungulate spongiform encephalopathy	Greater kudu, nyala, oryx, and others in zoos	Bovine spongiform encephalopathy prion contamination of meat-and-bone meal
Kuru	Humans	Ritual cannibalism in Fore people
Creutzfeldt–Jakob disease	Humans	<p>Iatrogenic—human prion contamination of dura mater grafts, therapeutic hormones, etc., all derived from cadavers</p> <p>Familial—germ line mutation in PrP gene</p> <p>Sporadic—unknown cause, perhaps somatic mutation in PrP gene or spontaneous conversion of PrP^C into PrP^{Sc}</p>
New-variant Creutzfeld–Jakob disease	Humans	Transmission of bovine spongiform encephalopathy prion to humans, unknown route, possibly by eating beef products
Gerstmann–Sträussler–Scheinker syndrome	Humans	Familial—germ line mutation in PrP gene
Fatal familial insomnia	Humans	Familial—germ line mutation in PrP gene

Replication of Prions

- It is the presence of horizontally or perhaps vertically transmitted PrP^{sc} that catalyzes the conversion of normally encoded PrP^c molecules into more PrP^{sc} molecules.
- While PrP^{sc} acts as the template, the "seed crystal," for the abnormal folding and polymerization of PrP^c forming a heterodimer with normal cellular PrP^c.
- There is evidence that another molecule, called protein X, is needed for prion replication when transmission occurs between distant host species.



Replication of Prions

- In any case, the process cascades exponentially, with newly formed PrP^{sc} in turn serving as a catalyst for the conversion of more and more PrP^c molecules as they are produced in target cells such as neurons.
- Eventually, so much PrP^{sc} builds up that it polymerizes, forming fibrillar masses that become visible as plaques and cause neuronal degeneration and neurological dysfunction via mechanisms that are as yet poorly understood.
- In a like manner, different isoforms of PrP^{sc} "breed true" and are perpetuated even in mixed infections



Prion Reproduction Mechanism

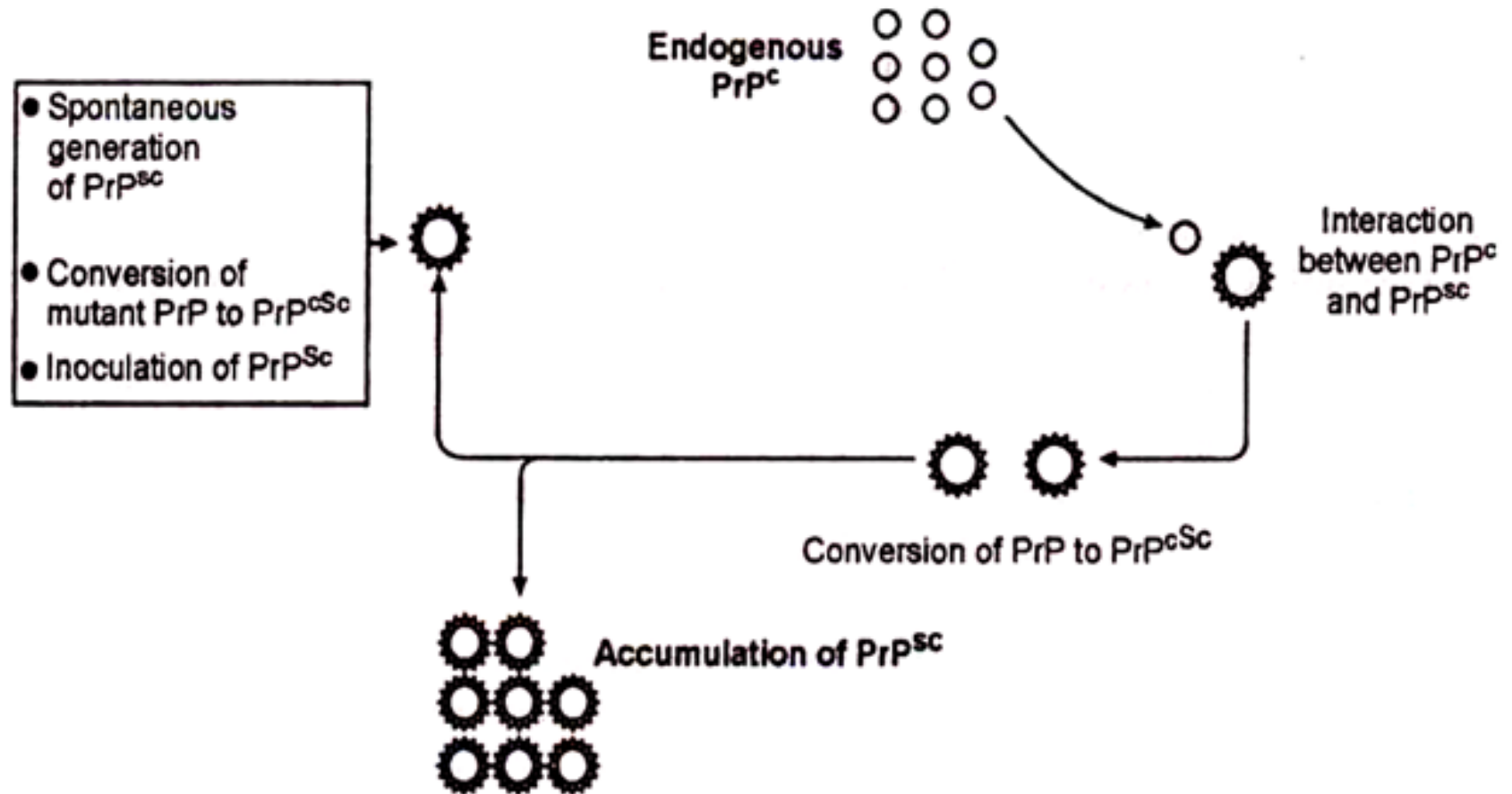


Fig. 3. Heterodimer model of prion propagation.



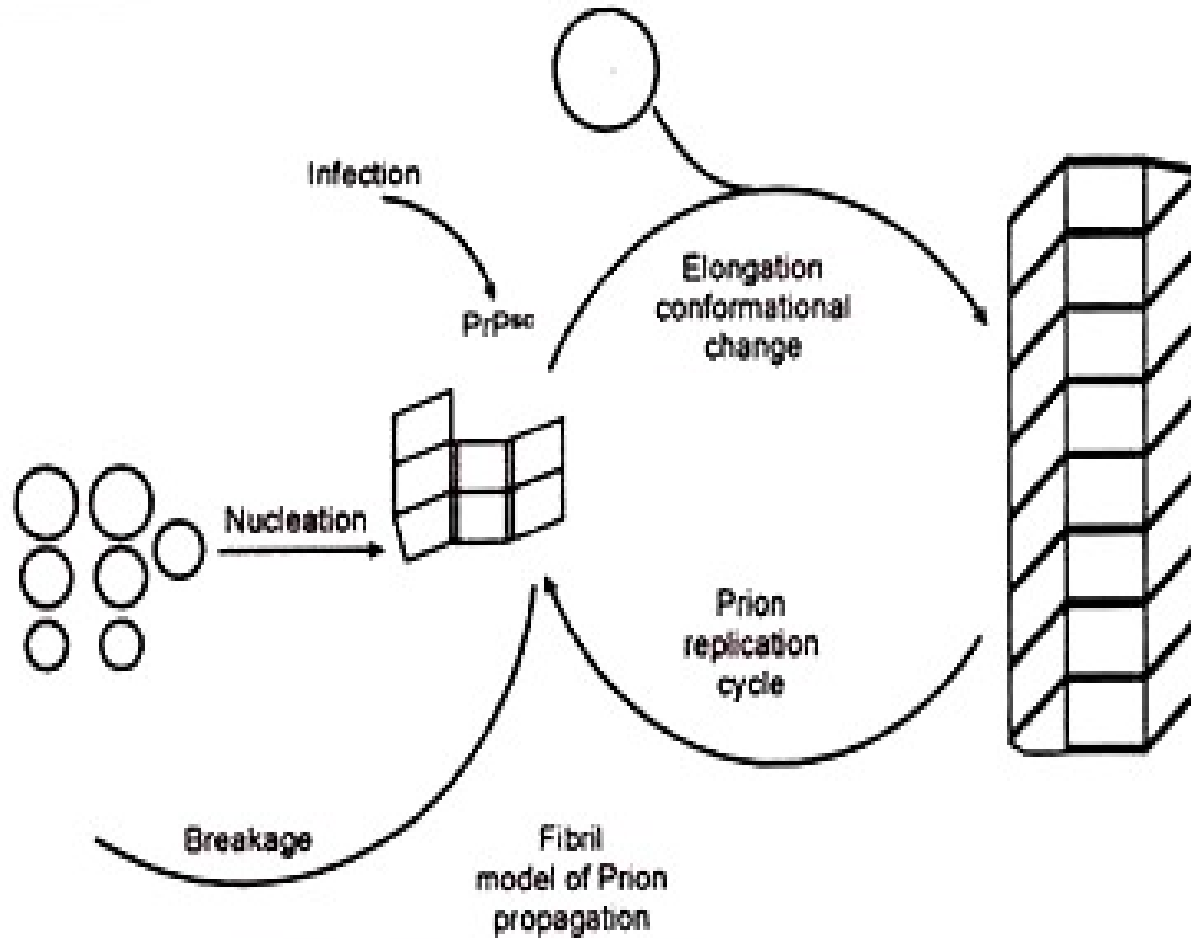


Fig. 4. Fibril model of Prion propagation.



SCRAPIE

- The incubation period of scrapie in sheep is 2-5 years and the onset of clinical disease is insidious.
- Affected sheep become excitable and develop fine tremors of the head and neck, which may be elicited by sudden noise or movement.
- Shortly thereafter, animals develop intense pruritus, with wool loss and skin rubbed raw.
- After 1-6 months of progressive deterioration, characterized by emaciation, weakness, weaving gait, staring eyes, ataxia, and hindquarter paralysis, animals invariably die.



- The first appearance of the scrapie prion in experimentally infected lambs occurs in the intestines, tonsils, spleen, and lymph nodes.
- Sequential infectivity titrations of organs have suggested that following the ingestion of prions, infection is initiated in gut lymphoid tissues and prions produced in these tissues then move to the central nervous system.
- At death, lesions in the gray matter of the brain include neuronal vacuolation and degeneration and astrocytic hypertrophy and hyperplasia.
- There is no inflammatory reaction or evidence of an immune response.



DIAGNOSIS

- Diagnosis is based on clinical signs, flock history, and histopathologic examination of the brain of suspect animals.
- Anti-PrP antibodies are used for immunohisto-chemical staining of suspect brain specimens and for Western blot assays of solubilized brain extracts and cerebrospinal fluid.
- The presence of PrP-containing plaques or PrP protein in the cerebrospinal fluid is considered diagnostic.
- No method is presently available for use on any practicably obtainable antemortem specimen, nor is any method useful in animals before the development of flank clinical signs of disease.



BOVINE SPONGIFORM ENCEPHALOPATHY

- Bovine spongiform encephalopathy was first recognized in the United Kingdom in 1986. By 1989, an alarming increase in the number of cases reported led to a ban on the feeding of meat-and-bone meal derived from ruminant meat or offal



BOVINE SPONGIFORM ENCEPHALOPATHY

- The onset of disease is insidious, with tremors, hyperaesthesia with kicking during milking, abnormal posture, hindlimb ataxia, progressive apprehensive behavior, aggression and even frenzy, reduced milk yield, and weight loss.
- The disease is inevitably fatal after a clinical course ranging from 2 to 3 weeks to over a year.
- Onset is independent of season or stage of lactation.
- Most cattle affected have been 3-5 years of age; older cattle have been affected and the youngest recorded case was 22 months of age.



BOVINE SPONGIFORM ENCEPHALOPATHY

- Pathologic changes are seen only in the brain.
- At death, lesions in the gray matter include neuronal vacuolation, neuronal degeneration and loss, and astrocytic hypertrophy and hyperplasia.
- There is no inflammatory reaction or evidence of an immune response.
- Lesions are most prominent in the nuclei of the midbrain, brain stem, and cervical spinal cord with minimal changes in cerebral cortex, cerebellum, hippocampus, and basal nuclei.



THANK YOU

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