PRIONS

Prions are proteinaceous infectious particles that do not utilize nucleic acids to mediate transmission. In other words, prions are infectious particle that consists only of protein. Prions are only known example of infectious pathogens that are devoid of nucleic acid. All other infectious agents, bacteria, viruses, fungi, protozoan, etc. possess genomes composed mostly of DNA or RNA that directs their multiplication. It was Prusiner in 1982, which isolated and characterized the infectious agent and coined the term "prion" (Prusiner got Nobel Prize in Medicine in 1997 for this work). It is well known for causing Transmissible spongiform encephalopathies (TSE's) also known as prion disease which is a type of degenerative disorders of the central nervous system leading to motor dysfunction, dementia and death. Prion diseases include scrapie of sheep, bovine spongiform encephalopathy (BSE) in cattle, and human diseases such as Creutzfeldt-Jakob disease (CJD), Gerstmann-Sträussler-Scheinker syndrome (GSS) and fatal familial insomnia (FFI). More recently, variant CJD (vCJD), ascribed to consumption of BSE-contaminated products, have claimed over 120 victims. Prion diseases are progressive neurodegenerative diseases of animals and humans which may be sporadic, genetic, or acquired. The pathologic mechanism of disease is not clear. Moreover, neither humoral nor cellular immunological responses have been detected in prion diseases.

Properties of prions

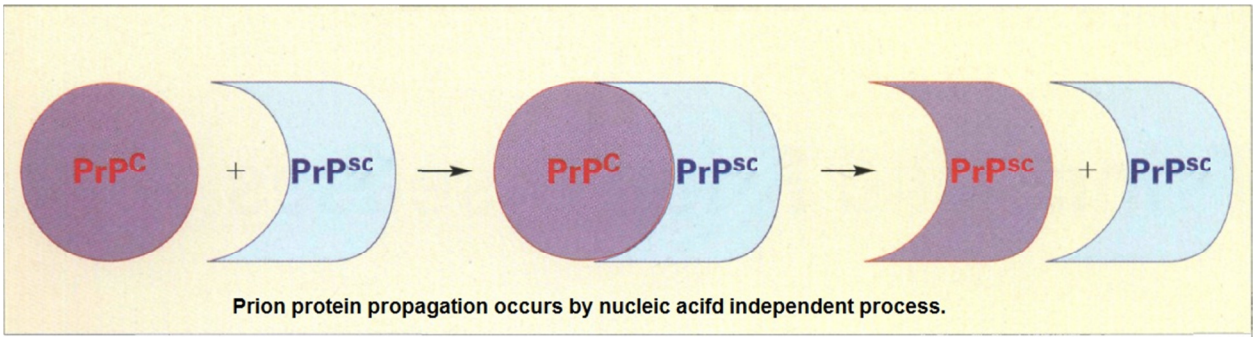
The proteinaceous infectious agent (Prion) consists primarily of a protein generally found in the membrane of normal cell that is known as prion protein cellular (PrP^c), but when these protein acquire an altered shape or conformation, it becomes disease causing isoform that is known as prion protein scrapie isoform PrP^{sc}. Prions reproduce by recruiting normal cellular prion protein (PrP^c) and stimulating its conversion to the disease-causing (scapie) isoform (PrP^{sc}), producing a chain reaction that propagates the disease and generates new infectious material. The process by which prions stimulate the conversion of PrP^c to PrP^{sc} is not clear.

The prions are resistant to most standard decontamination protocols. This mysterious infectious agent is resistant to ultraviolet radiation and X-rays, which breaks down nucleic acids, suggesting the absence of nucleic acid, but it is susceptible to substance that disrupt proteins. Interestingly, the disease causing isoform of prion protein is encoded by a chromosomal gene that makes it different from the virus. The gene for this protein is successfully cloned. Recent observations suggest a newer role of prions to transmit genetic trait from mother cells to daughter cells along through the cell cytoplasm in yeast *Sccharomyces sps*.

Biochemistry of Prions

Prions are composed of a unique protein called the prion protein (PrP). The normal neuronal cell surface form of PrP, PrP-cellular (PrP^c), is encoded by a single gene on human chromosome 20. The function of PrP^c is unknown, although studies have suggested a role in copper binding or possibly synaptic structure or function, but the relevance of these observation is unclear. Disease forming prions PrP^{sc} are similar in composition to cellular prion PrP^c but have marked differences in their three-dimensional conformation. Concurrent with the conformational alterations, new biochemical properties are acquired that are reflected in changes in detergent solubility, chemical stability, and resistance to enzymatic degradation, which form the basis for the detection of PrP^{sc}. The detection of prions has relied primarily on animal transmission studies or immunologic methods which require separation PrP^{sc} of from PrP^c because antibodies have

not been available that specifically and selectively detect only PrP^{sc}. However, Korth et al[1] reported a monoclonal antibody that apparently recognizes a conformational-dependent epitope on PrP^{sc}. The availability of such an antibody may greatly facilitate laboratory diagnosis of the prion disease.



Prions propagate by a unique mechanism. Unlike bacteria or viruses that rely on nucleic acid genetic material, prions convert preexisting PrP^{c} to PrP^{sc}. The initial PrP^{sc} maybe either exogenous, as in the infectious forms, or from the spontaneous conversion of endogenous PrP^{c} to PrP^{sc}, as in the more common sporadic disease. Observations from a number of sources suggest this it occurs either on the plasma membrane or an early endocytic compartment. It has been evident by various studies that mice PrP^{c} do not develop prion diseases or produce PrP^{sc}.

Structure of Prion

The human prion protein (huPrP) gene encodes a proto-protein of 253 amino acids long before processing. In the mature form, the first 22 residues are cleaved after translation, whereas the last 23 amino acid residues are cleaved prior to the addition of a glycosyl phosphoinositol (GPI)

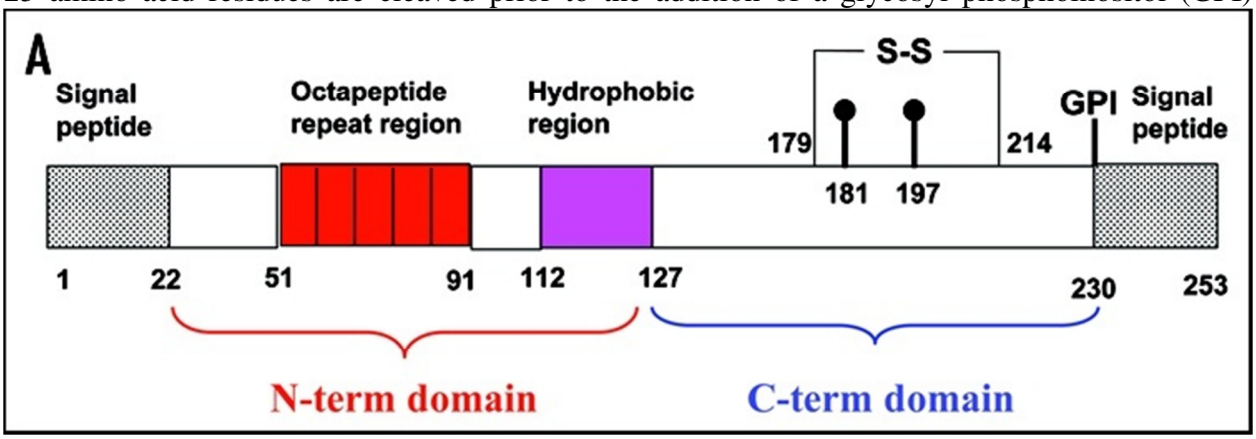


Figure: Block diagram of the huPrP gene organization. The positions of the glycosilation sites are indicated at Asn181 and Asn197. Cys179 (Cysteine179) is covalently bound to Cys214. The number of octarepeats depends on the species considered.

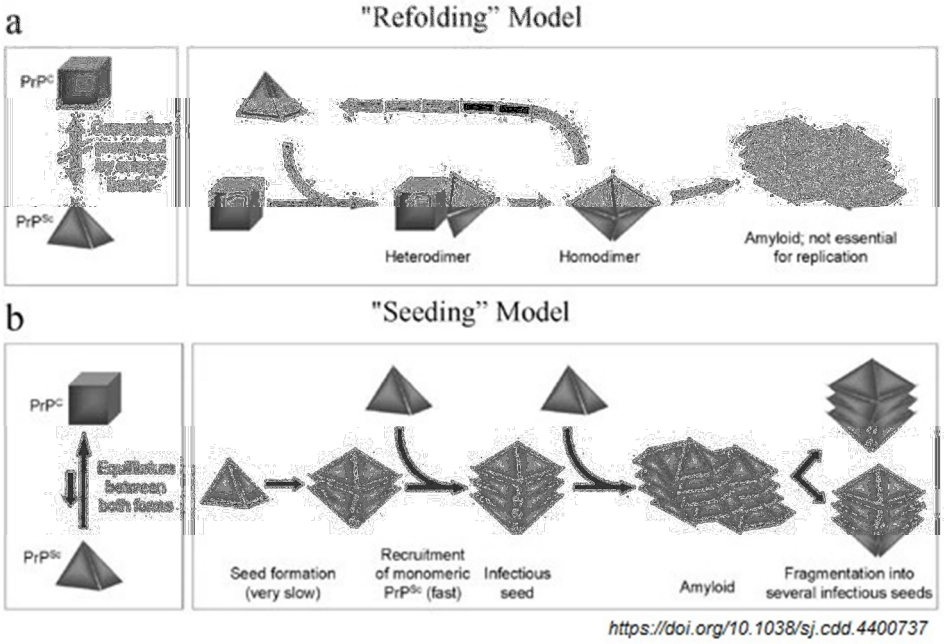
anchor to Ser230. PrP are extracellular proteins of total 198 amino acid residues normally attached to the outer surface of the cellular membrane by means of the GPI anchor. They have also two N-linked glycosylation sites at residues Asn181 (Asparagine181) and Asn197. They are highly conserved amongst mammals: huPrP has 94.9%, 99.2% and 92.8% sequence identity with the protein from sheep, chimpanzee and cow respectively. More distant but still highly

[1] Korth C et al. Prion (PrP^{sc})-specific epitope defined by a monoclonal antibody. Nature 1997; 390: 74-77.

homologous orthologues (30% identity and 50% similarity) are present in reptiles and amphibians.

PrP^C is divided into two regions with distinct structural and dynamical properties. In mammals, the N-terminus hosts a variable number (depending on the organism) of octapeptide PHGGSWGQ repeats. Each octarepeat is able to bind divalent metals such as copper and others, although the physiological significance of this interaction remains unclear. The octarepeats in mammalian PrPs are hexarepeats in birds and reptiles and a not readily apparent repeat pattern in frogs. The N-terminus domain possibly acquires a loop and β-turn-like conformation at pH 6.2. An increase in the population of transient secondary or tertiary structure is observed on increase in pH value. The C-terminus of PrP is structured and presents a globular fold of three α-helices (H1, H2 and H3) and a short, double-stranded, antiparallel β-sheet (S1, S2). A disulfide bridge between Cys179 and Cys214 links H2 and H3.

In a nut shell, cellular prion protein (PrP^c) is rich in alpha-helixes (spiral-like formations of amino acids) and has little beta-sheet (flattened strands of amino acids), whereas disease causing prion protein (PrP^{sc}) is less rich in alpha-helixes and has much more beta-sheets. The structural transition from alpha-helixes to beta-sheet in PrP is said to be the fundamental event underlying prion disease. There are two models namely refolding model and seeding model to show the conversion of PrP^c to PrP^{sc} by changes in conformation of these proteins as shown in figure.



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"Refolding" model (a. in figure) or template assistance model postulates an interaction between exogenously introduced PrP^{sc} and endogenous PrP^c which is induced to transform itself into further PrP^{sc}. It is kinetically controlled endogenous process, where a high activation energy barrier prevents spontaneous conversion from PrP^c to PrP^{sc}.

"Seeding" or nucleation-polymerization model proposes that PrP^c and PrP^{sc} molecules are in reversible thermodynamic equilibrium, with strongly PrP^c favored. PrP^{sc} is only stabilized when it adds onto a crystal-like highly ordered seed, where further monomeric PrP^{sc} can be recruited and eventually aggregates to amyloid. Seed formation is said to be a rare event, however once a seed is present, monomer addition ensues rapidly.

Pathogenesis of Prion

Histopathologic findings suggest that it consist of neuronal loss, numerous fine vacuoles (spongiform degeneration), and reactive astrogliosis (nonspecific reactive response of brain astrocytes). In an animal model, immunohistochemical studies show that PrP^{sc} accumulation precedes, and colocalizes with, the development of the pathologic lesions.

The prion diseases

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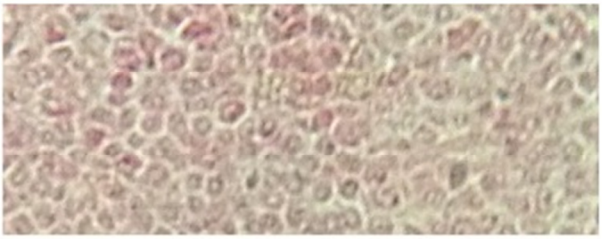
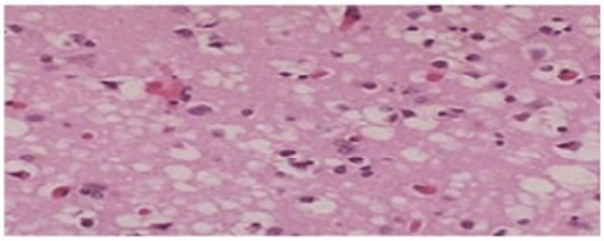
Disease	Host	Mechanism of pathogenesis
iCJD	humans	infection from priom-contaminated hGH, dura mater grafts, etc.
nvCJD	humans	infection from BSE prions (hyphothesized)
fCJD	humans	germ-line mutations in *PRNP* gene
sCJD	humans	somatic mutation resulting in spontaneous conversion of PrP^{C} into PrP^{Sc}
Kuru	fore people	infection through ritualistic cannibalism
GSS	humans	germ-line mutations in *PRNP* gene
FFI	humans	germ-line mutations in *PRNP* gene
FSI	humans	somatic mutation resulting in spontaneous conversion of PrP^{C} into PrP^{Sc}
Scrapie	sheep	infection in genetically susceptible sheep
BSE	cattle	infection with prion-contaminated MBM
TME	mink	infection with prions from sheep or cattle
CWD	mule, deer, elk	Unknown
FSE	cats	infection with prion-contaminated bovine tissues or MBM
Exotic ungulate encephalopathy	greater kudu, nyala, oryx	infection with prion-contaminated MBM

iCJD, iatrogenic CJD; nvCJD, new variant CJD; fCJD, familial CJD; sCJD, sporadic CJD; GSS, Gerstmann-Sträussler-Scheinker disease; FFI, fatal familial insomnia; FSI, fatal sporadic insomnia; BSE, bovine spongiform encephalopathy ('mad cow disease'); TME, transmissible mink encephalopathy; CWD, chronic wasting disease; FSE, feline spongiform encephalopathy; hGH, human growth hormone; MBM, meat and bone meal

The routes of infection in natural and experimental prion diseases comprise uptake of prions via the alimentary tract or through scarification of gums, skin, and conjunctiva, or intracerebral, intraperitoneal, intramuscular, or intravenous inoculation. Spread of the agent depends on their site of entry, strain, dose, and species and PrP genotype of the host. It has been drawn that after oral uptake, prions may penetrate the intestinal mucosa through M cells and reach Peyer's patches as well as the enteric nervous system. Depending on the host, prions may replicate and accumulate in spleen and lymph nodes. Myeloid dendritic cells are thought to mediate transport within the lymphoreticular system. From the lymphoreticular system and likely from other sites prions proceed along the peripheral nervous system to finally reach the brain, either directly via the vagus nerve or via the spinal cord, under involvement of the sympathetic nervous system.



Normal brain tissue



Sponge-like lesions in the brain tissue of a CJD patient

Its infection leads to synaptic degeneration and loss which is ultimately precede with neuronal degeneration, in particular since both PrP^{c} and PrP^{sc} are located to synapses. Recently lprogressive loss of dendritic spines of neuronal cells has been observed. In various forms of prion diseases under study suggests that pathogenesis by prion resultant of cell death among neuronal cells possibly by activating caspase-3 enzyme that results in onset of apoptotic pathway. Another cell death process, autophagy, is also present as evident from the presence of

autophagic vacuoles in experimentally induced scrapie, CJD, GSS, and FFI. Further studies showed that oxidative stress is a global event in prion disease affecting various types of neurons, while there seems to be some selective neuronal vulnerability (e.g. of parvalbumin immunoreactive GABAergic neurons). Further, it has been proposed that PrP^{sc} aggregates or amyloid may act as neurotoxin that may cause pathogenesis of prion molecule.

Prevention and treatment of Prion diseases

Prion diseases are different from most other types of diseases. Prions can act like an infection as they travel from cell to cell in a person's body, yet unlike viruses or bacteria, they have no DNA or RNA – they're just made of protein. There has never before been a treatment for a disease like this, so right now it isn't yet clear which strategy will ultimately lead to a treatment or cure. However, some strategies have been tried to develop using small molecules and antibodies.

Small molecules: Small molecules are those molecules which is small in size and easy to administer. Small molecules such as cpd-b, IND24, and anle138b are under study with initial positive results.

Antibody: Antibody might probed to be a promising and effective candidate against prion infection. Laboratory results indicate that monoclonal antibody against the prion protein can cure prion infected animals. The MRC Prion Unit in London is trying to launch a clinical trial by preparing anti-PrP antibody named PRN100 for the treatment of sporadic Creutzfeldt-Jakob disease. However, anti-PrP antibody to work, it has to pass blood-brain barrier

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