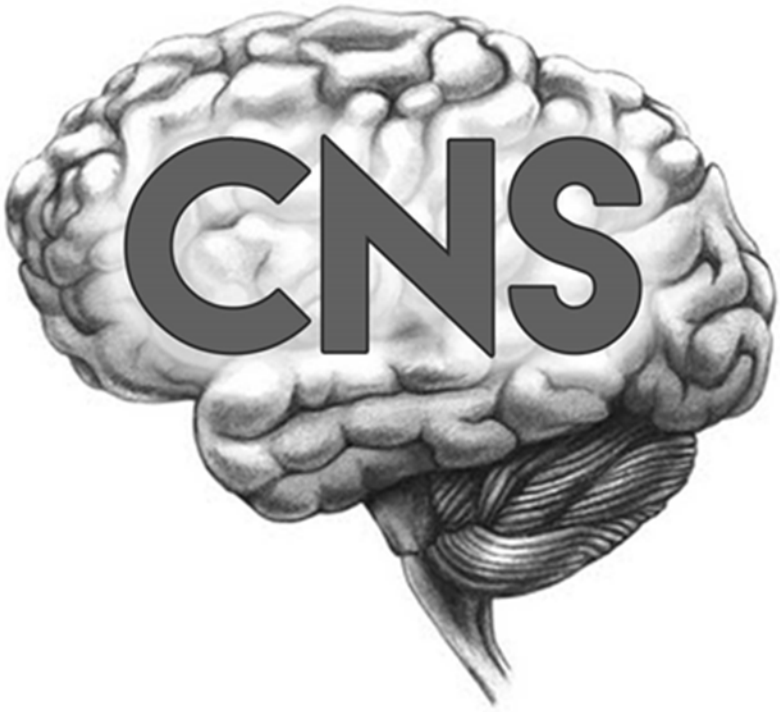


MICROBIOLOGY

○ Sheet ☑ Slide ○ Handout

Number

4

Subject

Prions

Doctor

Ashraf

Date: **00/00/2016**

Price:

Prions

Prions

- Prions are rather ill-defined infectious agents believed to consist of a single type of protein molecule with no nucleic acid component. Confusion arises from the fact that the prion protein & the gene which encodes it are also found in normal 'uninfected' cells. These agents are associated with diseases such as Creutzfeldt-Jakob disease in humans, scrapie in sheep & bovine spongiform encephalopathy (BSE) in cattle.

Definition

Prions are proteinaceous transmissible pathogens responsible for a series of fatal neurodegenerative diseases (in humans, Creutzfeld-Jakob disease and kuru, in animals, bovine spongioform encephalopathy)

A prion (**pro**teinaceous **in**fectious particle, analogy for virion) is a type of infectious agent that does not carry the genetic information in nucleid acid!

Prions are proteins with the pathological conformation that are believed to infect and propagate the conformational changes of the native proteins into the the abnormally srtructured form

Prion history

In the**1960s**: some TSEs are caused by an infectious agent made solely of protein; it is ultraviolet radiation (that breaks down nucleid acids present in viruses and all living things) resistent

In **1982**: Stanley B. Prusiner purified infectious material and confirmed that the infectious agent consisted mainly of a specific protease resistent protein; he coined the word "prion" as a name for the infectious agent (proteinaceous infectious particle); he received the Nobel Prize in 1997

Further research: the protein that prions are made of is found throughout the body, even in healthy people and animals; the prion protein found in infectious material has a different structure and is resistant to proteases

Normal prion protein is found on the membranes of cells, though its function has not been fully resolved; its gene has been isolated (some prion diseases can be inherited, the mutations make PrP^{C} more likely to spontaneously change into the PrP^{Sc})

The mechanism of prion infection and propagation remains mysterious (replication cycle)

The prion hypothesis was initially highly controversial, because it seemed to contradict the so-called „central dogma of modern biology," which asserts that all living organisms use nucleic acids to reproduce

The "protein-only hypothesis„: a protein structure could reproduce itself in the absence of DNA

In January **2007**: Yale University scientists have challenged this explanation for the disease asserting that they've found a virus responsible for the diseases

Disease name	Natural host	Prion name	PrP isoform
Scrapie	Sheep, goat	Scrapie prion	$OvPrP^{Sc}$
Transmissible mink encephalopathy (TME)	Mink	TME prion	$MkPrP^{Sc}$
Chronic wasting disease (CWD)	Elk, mule deer	CWD prion	$MDePrP^{Sc}$
Bovine spongioform encephalopathy (BSE)	Cattle	BSE prion	$BovPrP^{Sc}$
Feline spongioform encephalopathy (FSE)	Cat	FSE prion	$FePrP^{Sc}$
Exotic unguale encephalopathy (EUE)	Greater kudu, nyala	EUE prion	$NyaPrP^{Sc}$
Kuru	Human	Kuru prion	$HuPrP^{Sc}$
Creutzfeldt-Jakob disease (CJD)	Human	CJD prion	$HuPrP^{Sc}$
Gerstmann-Straussler-Scheinker syndrome (GSS)	Human	GSS prion	$HuPrP^{Sc}$
Fatal familial insomnia (FFI)	Human	FFI prion	$HuPrP^{Sc}$

Prion diseases: rare neurodegenerative disorders (one person per million)

1. Sporadic (85 %)

In the sixth or seventh decade, rapidly progressive (death in less than a year)

Creutzfeldt-Jakob disease (CJD)

2. Familial (inherited-15%)

Mutations in the PrP gene that favour the transition from the cellular form to the pathological form of PrP

Gerstmann-Straussler-Scheinker disease (GSS), fatal familial insomnia (FFI)

3. Transmissible (rare; a source of great concern)

Propagation of kuru disease in New Guinea natives (ritualistic cannibalism)

Recently, it has been discovered that BSE had been transmitted to humans in Europe after consumption of infected beef, producing a variant of the CJD called vCJD

Transmissible spongioform encephalopathy (TSE)=prion disease

A group of progressive conditions that affect the brain and nervous system of humans and animals and are transmitted by prions

The pathology: vacuolar degeneration, neuronal loss, astrocytosis and amyloid plaque formation

The clinical signs: loss of motor functions (lack of coordination, ataxia, involuntary jerking movements), personality changes, depression, insomnia, confusion, memory problems, dementia, progressive tonic paralysis, death

Definitive diagnostic test: biopsy of brain tissue (histopathological examination and immunostaining for $PrP^{Sc)}$

There is no cure

Prion transmission

1. Direct contact with infected tissues

CJD has been transmitted:

- To patients taking injections of growth hormone harvested from human pituitary glands
- From instruments used for brain surgery (prions can survive the autoclave sterilization process)
- In corneal grafts
- In electrode implants

2. Consumption of affected tissues

Kuru was transmitted through cannibalism in Papua New Guinea

Humans can contract the disease by consuming material from animals infected with the BSE (vCJD)

How can prions make their way through the gut and into the brain?

Proteins normally are digested down to amino acids in the gut

Hypothesis: They circumvent the normal process of intestinal absorption by passing into the the Gut-Associated Lymphoid Tissue (GALT)

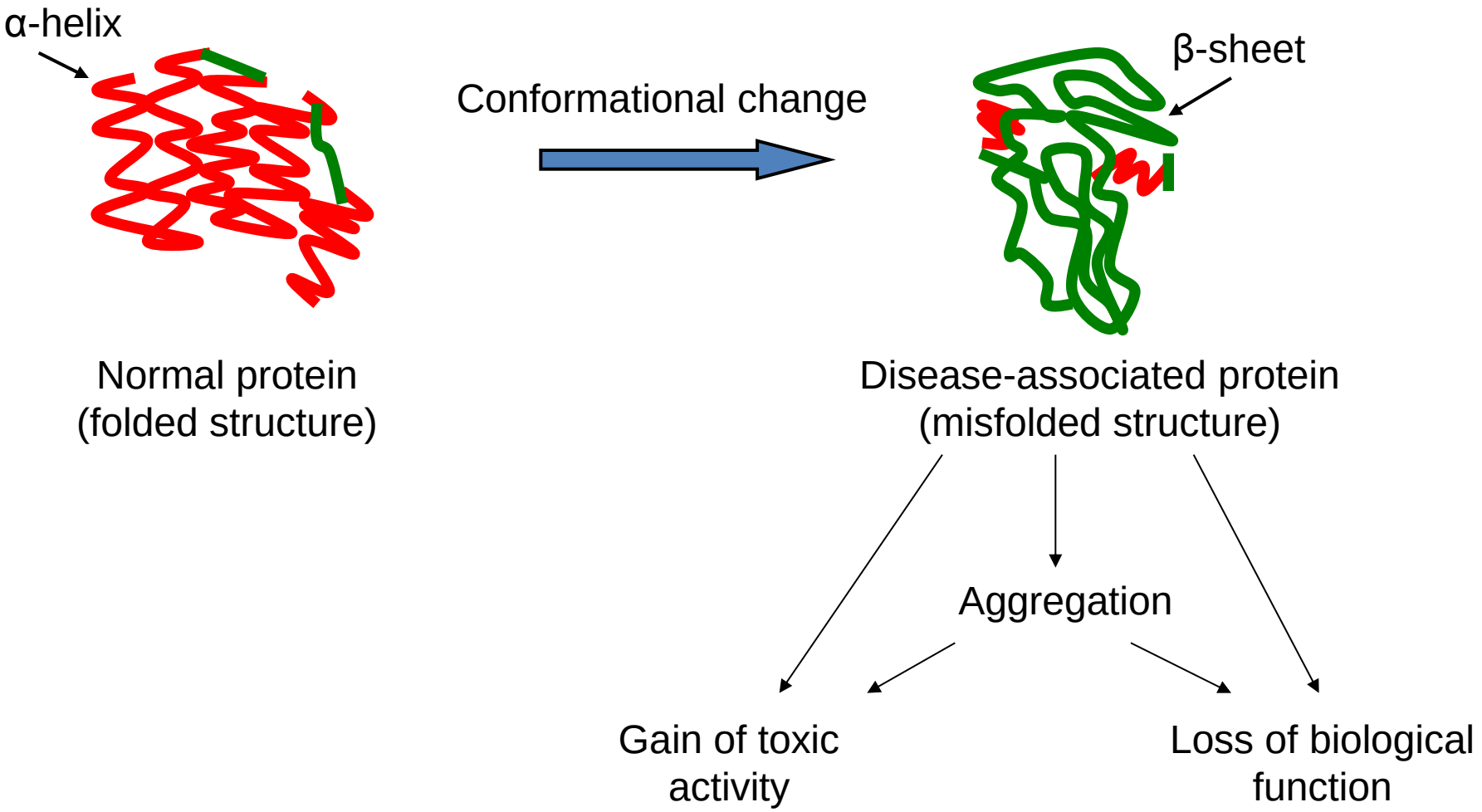
Protein misfolding diseases

Arise from abnormal conformation of specific proteins

Principle: Proteins can adopt an aberrant conformation that cause disease; two mechanisms must be considered: loss of function of the native protein or gain of toxic activity of the aberrant conformation

More than 20 human pathologies

Prion diseases arise from the harmful function of the abnormal proteins; misfolded forms of proteins (rich in β-sheet structures) have a strong propensity to aggregate into insoluble material and form fibrils


α-helix
Conformational change
β-sheet
Normal protein
(folded structure)
Disease-associated protein
(misfolded structure)
Aggregation
Gain of toxic
activity
Loss of biological
function

Genetics of prion disease

Familial forms of prion disease are caused by inherited mutations in the PRNP gene

Mutations in this gene cause cells to produce an abnormal form of the prion protein, known as PrP^{Sc}

Most cases of prion disease are sporadic, they occur in people without gene mutations

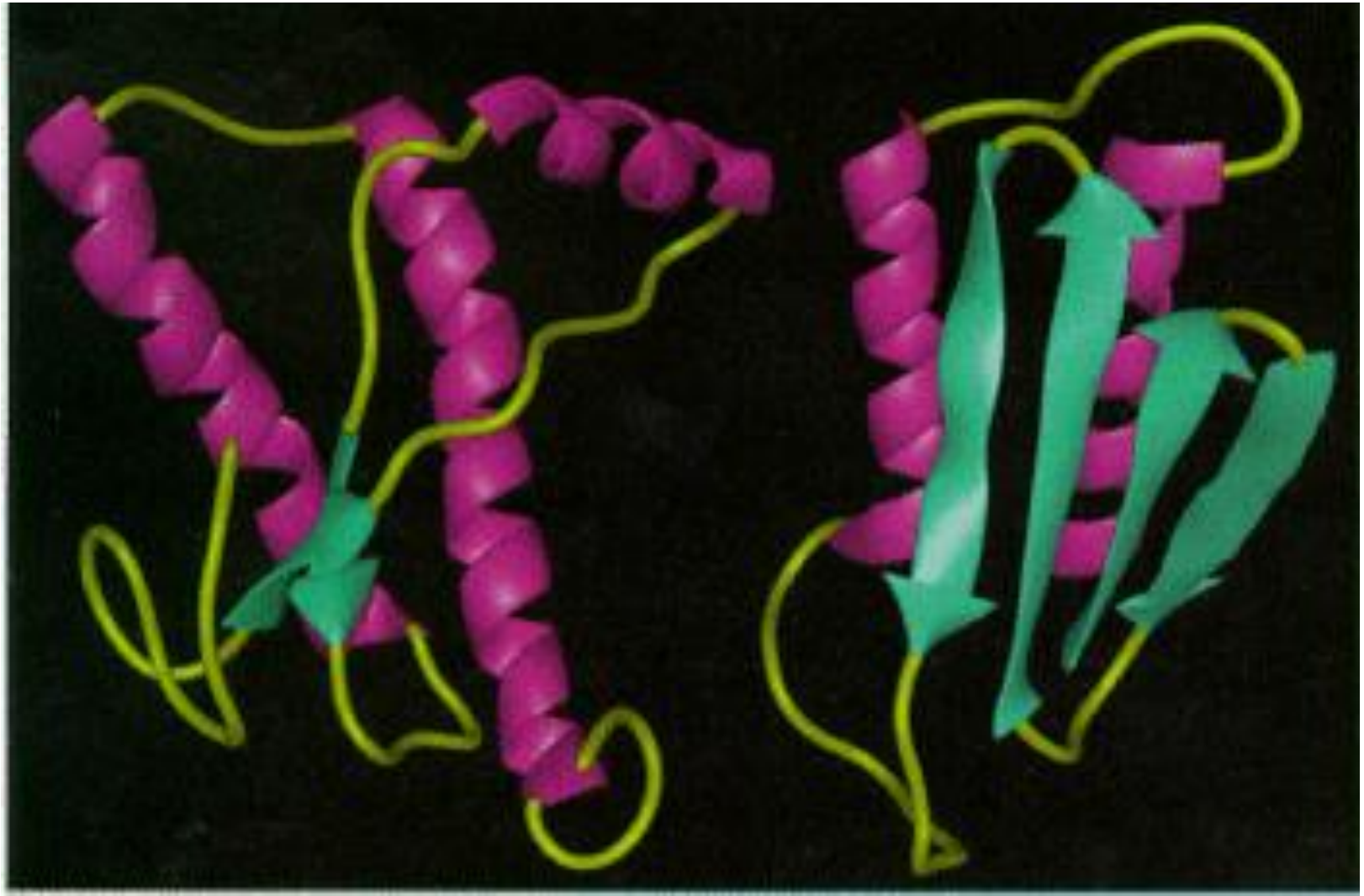
Familial forms of prion disease are inherited in an autosomal dominant pattern

PrP^{C}	PrP^{Sc}
The normal protein	**The abnormal, disease-producing protein**
is called PrP^{C} (for cellular)	**is called PrP^{Sc} (for scrapie)**
is a transmembrane glycoprotein (neurons, lymphocytes); its function is unknown	**has the same amino acid sequence (primary structure)**
has dominant secundary structure α-helix	**has dominant secundary structure β-sheets**
is easily soluble	**is insoluble**
is monomeric and easily digested by proteases	**is multimeric and resistant to digestion by proteases**
is encoded by a gene designated PRNP located on the chromosome 20	**When PrP^{Sc} comes in contact with PrP^{C}, it converts the PrP^{C} into more of itself These molecules bind to each other forming aggregates**

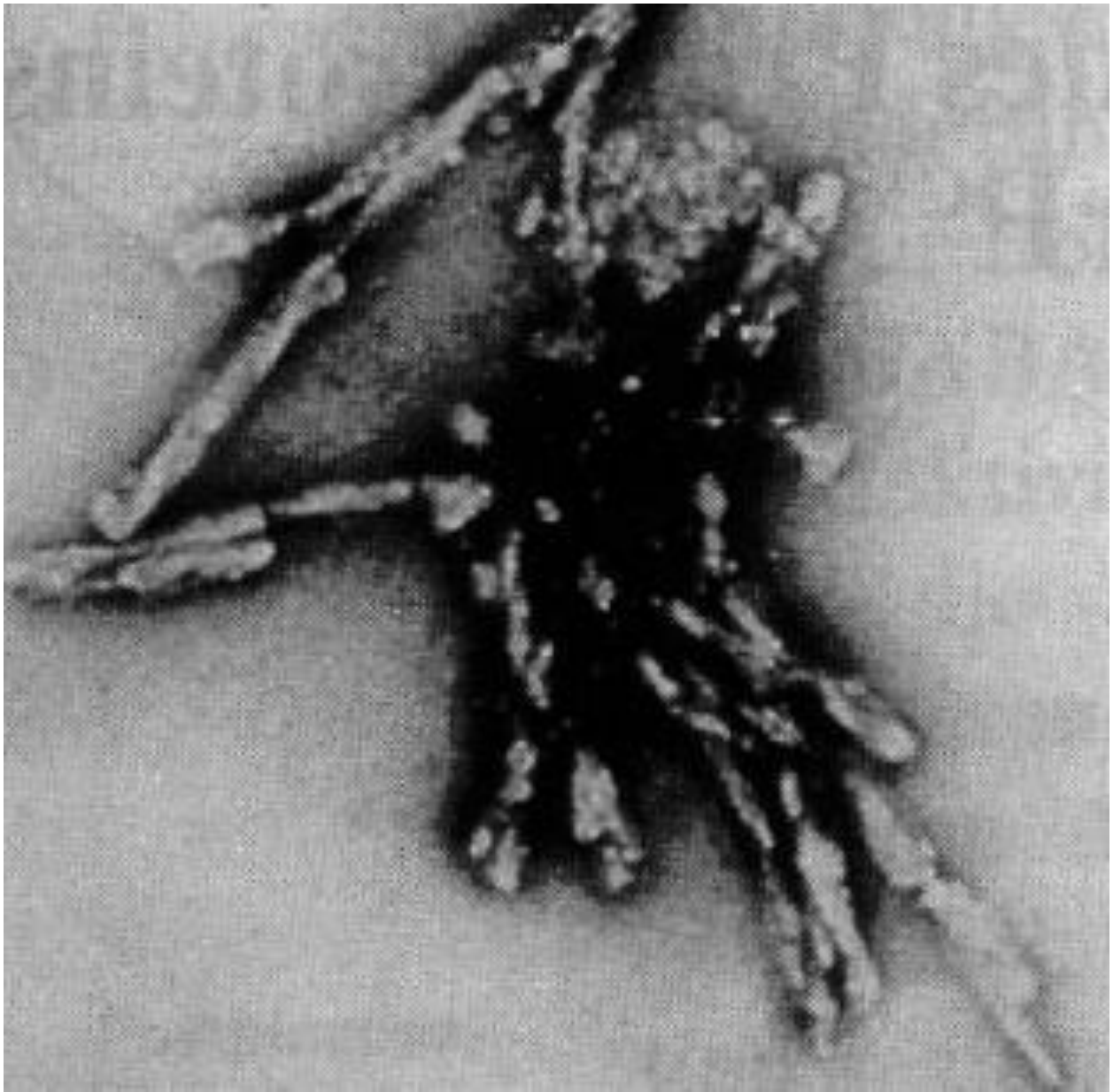
Molecular models of the structure of:

PrP^{C} **PrP^{Sc}**

Predominantly α-helix (3) β-sheets (40%), α-helix (30%)



Prion aggregates (an electron microscope picture)

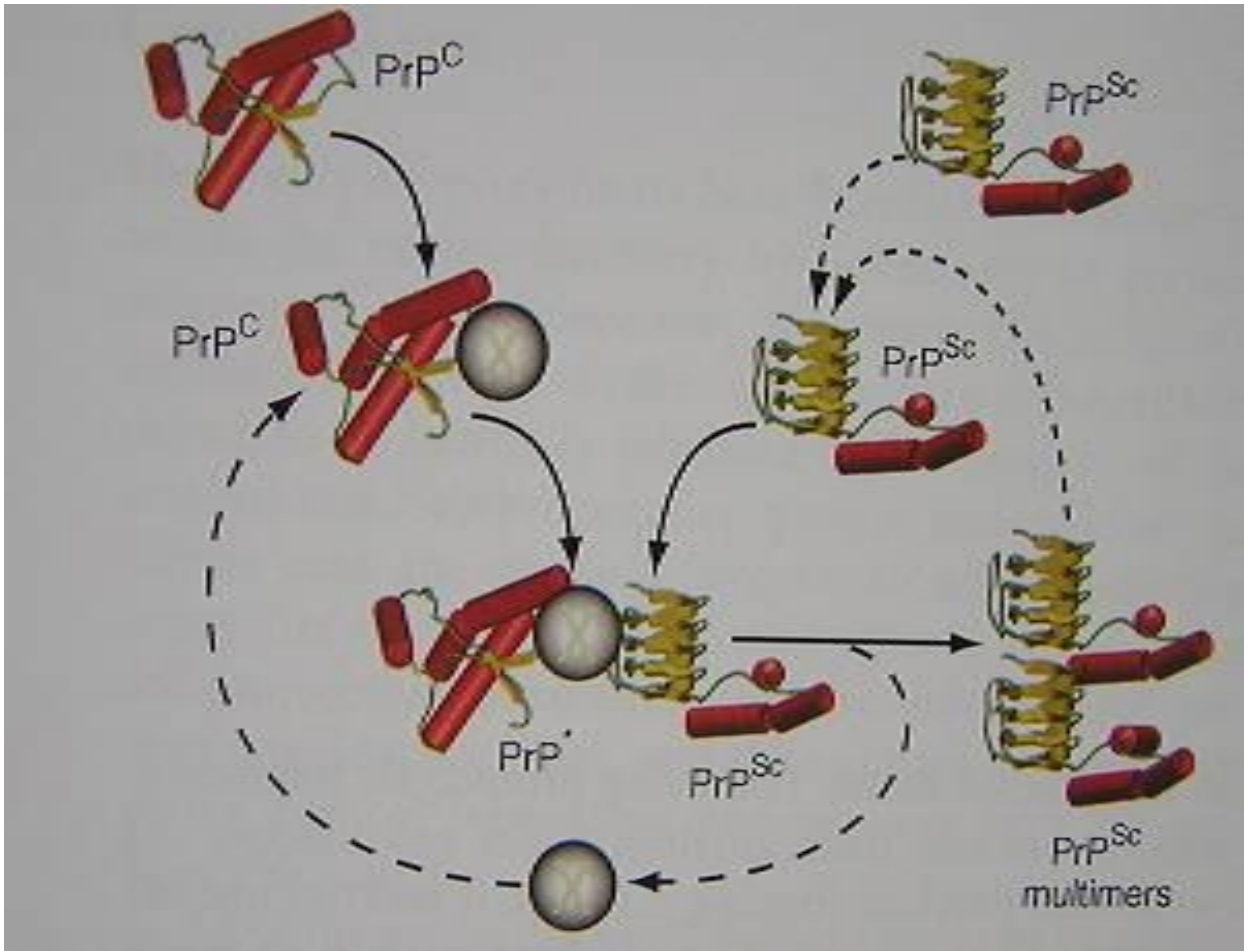


Replication cycle

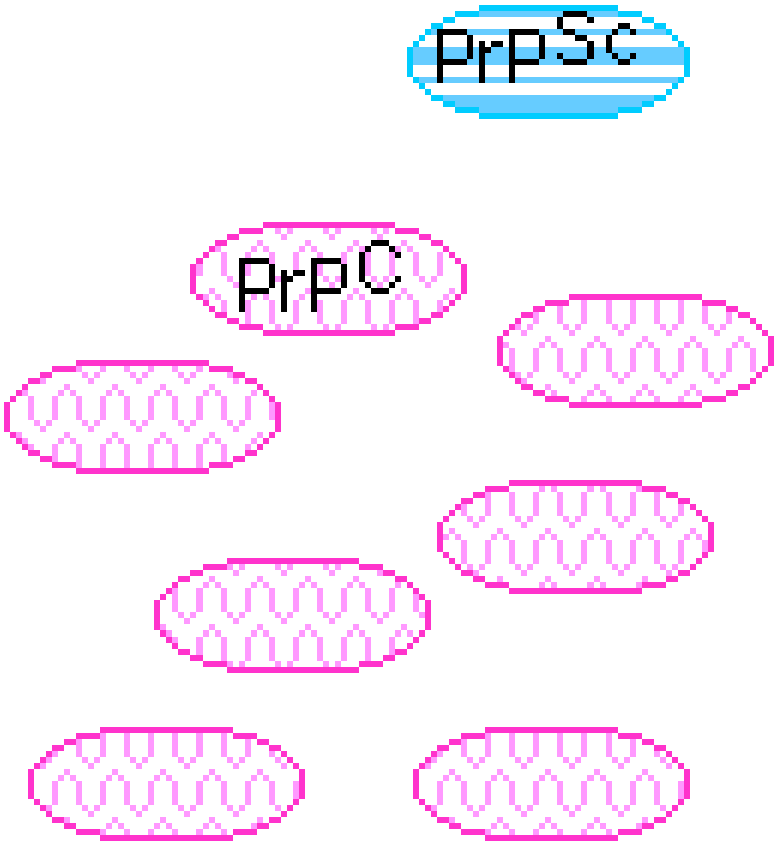
The presence of an initial PrP^{Sc}: exogenous (infectious forms) or endogenous (inherited or sporadic forms)

This first prion will initiate PrP^{Sc} accumulation by sequentially converting PrP^{C} molecules into PrP^{Sc} in replication cycle

PrP^{Sc} molecules aggregate



Mechanism of prion progression



Kuru (a native word meaning “trembling with cold and fever“)

Is a prion disease incident in natives in New Guinea

(first noted in the early 1900s)

In 1950-60 epidemic

Cannibalism: relatives ate their dead relative's brains as a sign of mourning

In the 1950's, the practice was banned, thereby preventing any further possible transmission; (incubation period of 4 to 20 years)

Symptoms: 3 stages; gradually deterioration of motor and mental functions

The first stage, exhibits unsteady gait, decreased muscle control, tremors, deterioration of speech and dysarthria (slurred speech).

second stage, incapable of walking without support, suffers ataxia (loss of muscle coordination), severe tremors and depression.

final stage, the patient suffers severe ataxia, is unable to speak, is incontinent, has dysphagia (starvation), is unresponsive to their surroundings

An infected person usually dies within 3 months to 2 years after the first symptoms, often because of pneumonia or pressure sores infection

Creutzfeldt-Jakob disease (CJD)

is the most common of the prion disease

usually affects people aged 55-65 (vCJD occurs in younger people)

The duration of CJD is less than 1 year

Symptoms: Dementia, hallucinations, motoric dysfunction, ataxia and seizure

Diagnosis: symptoms, EEG, MRI, CSF analysis

The definitive diagnostic test: biopsy of brain tissue

Treatment: fatal disease, searching for viable treatments

Forms:

1. Sporadic
2. Familial
3. Transmitted: iatrogenic-iCJD, via consuming -vCJD

Blood donor restrictions: prions can be transmitted by blood transfusions; there is no test to determine if a blood donor is infected; restrictions for blood donors

Characteristic	Classic CJD	Variant CJD
Median age at death	68 years	28 years
Median duration of illness	4-5 months	13-14 months
Clinical signs and symptoms	Dementia; early neurologic signs	Prominent psychiatric/behavioral symptoms; delayed neurologic signs; hallucinations
Specific changes on MRI	Often present	Often present
Specific changes on EEG	Often present	Often absent
Immunohistochemical analysis of brain tissue	Variable accumulation of the PrP^{Sc}	Marked accumulation of the PrP^{Sc}
Presence of agent in lymphoid tissue	Not readily detected	Readily detected
Presence of amyloid plaques in brain tissue	Often present	Often present

Diagnosis

- Gold standard: brain biopsy (histopathological examination and immunostaining for $PrP^{Sc)}$
- CSF: elevated protein 14-3-3 and S100
- CT and MRI: Normal, if abnormal not diagnostic
- EEG: abnormal pattern in 2/3 of Creutzfieldt-Jakob disease

Therapeutic strategies

1. Compounds can be designed to specifically disrupt the replication cycle of the PrP^{Sc}

Design of such compounds had proven successful in cell-based models but must now be extended to animal models and human clinical trials

2. Vaccine design: The abnormally folded proteins expose a side chain of amino acids which the properly folded protein does not expose. Antibodies specifically coded to this side chain amino acid sequence stimulate an immune response to the abnormal prions

3. Design of peptides that break the β-sheet structures

4. Gene therapy: modification of the prion gene

Genetic engineering research: cattle lacking a necessary gene for prion production - thus theoretically making them immune to BSE (December 2006)

Summary

The prions are proteins that carry information for self-reproduction (contradict the central dogma of modern biology)

The prions are expressed in cells of healthy humans and animals; their abnormal conformations (PrP^{Sc}) are insoluble, resistent to digestion and aggregate

The PrP^{Sc} attacks the native prion PrP^{C}, changes its conformation into an abnormal form and causes an exponential production of insoluble proteins; they aggregate and form the fibrillar structure

Prion disease are rare fatal degenerative disorders; a portion of them can be transmitted; this mechanism is not clear (e.g. transmision of BSE to human)

One part of the prion protein can cause apoptosis, or programmed cell death

Prions induce no immune reactions within the human