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Creutzfeldt-Jakob as an Example of Prion Disease: I. Prions

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Abstract

Creutzfeldt–Jakob disease (CJD) is a rare, incurable, and always fatal neurodegenerative disease. It belongs to a class of human and animal diseases known as prion diseases. A prion is a misfolded protein which induces misfolding in normal variants of the same protein, leading to cellular death. Prions are also linked to other neurodegenerative diseases like Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis, which are sometimes referred to as prion-like diseases. In this introductory article, after a brief foray into their history, prions will be presented in terms of their nature, structure, normal functions, propagation, degradation, replication and implications for drug design as well as their links to and roles in other neurodegenerative diseases. Bypassing the traditional flow of genetic information within a biological system, primarily from DNA to RNA to protein, prions have forced a reconsideration of the central dogma of biology – a topic addressed in a sidebar.

Abbreviations

AD: Alzheimer's disease; ALS: Amyotrophic lateral sclerosis; BSE: Bovine spongiform encephalopathy; CD: Crohn's disease; CJD: Creutzfeldt-Jakob disease [including aCJD: acquired; iCJD: iatrophic; fCJD: familial; sCJD: sporadic]; CNS: Central nervous system;; CWD: Chronic wasting syndrome; FTLD-U: Frontotemporal degeneration with ubiquitin-positive inclusions; GSSS: Gerstmann-Straussler-Scheinker syndrome; HD: Huntington's disease; HNR: Heterogeneous nuclear riboproteins; HEN: Homing endonuclease; MCD: Mad cow disease; MM: Methionine/methionine; MSA: Multiple system atrophy; MV: Methionine/valine; PD: Parkinson's disease; PrLD: Prion-like domain; PrP: Prion protein; RA: Rheumatoid arthritis; TAR: Transactive response; TDP: Transactive response DNA-binding protein; TSE:

Transmissible spongiform encephalopathy; UPS: Ubiquitin proteosome system.

Keywords

Creutzfeldt-Jakob disease; prions; prion degradation; prion links to neurodegenerative diseases; prion protein functions; prion replication models; prion transmission; transmissible spongiform encephalopathy.

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Introduction

Creutzfeldt–Jakob disease (CJD) is a rare, incurable, and always fatal neurodegenerative disease. It belongs to a class of human and animal diseases known as prion diseases. It received public attention in the 1990s when some people in the United Kingdom became sick with a form of the disease called variant or CJD (vCJD) after eating meat from diseased cattle. However, most CJD cases have not been linked to such a cause. There are three 3 other forms of the disease: sporadic (sCJD), acquired (aCJD), and genetic or familial (g/fCJD).

All types of CJD are serious but are very rare - about 1 to 2 cases are diagnosed per million people around the world each year. The disease most often affects older adults. About 85% of cases of CJD occur for unknown reasons, while about 7.5% of cases are inherited in an autosomal dominant matter. However, vCJD affects people at a younger age and appears to last 12 to 14 months. Exposure to brain or spinal tissue from an infected person may also result in its spread. There is no evidence that sCJD can spread among people via normal contact or blood transfusions, although this is possible in vCJD.

CJD is caused by prions. Infectious prions are misfolded proteins that occur in the neurons of the central nervous system (CNS) and can cause normally folded proteins to also become misfolded. The CJD prion is dangerous because it promotes refolding of the cellular prion protein into the diseased state. The number of misfolded protein molecules will increase exponentially, and the process leads to a large quantity of insoluble protein in affected cells. This mass of misfolded proteins disrupts neuronal cell function and causes cell death. Once the prion is transmitted, the defective proteins invade the brain and induce other prion protein molecules to misfold in a self-sustaining feedback loop. These neurodegenerative diseases are commonly called prion diseases.

To understand CJD, it will be helpful to first learn more about prions, the subject of this introductory article.

A brief foray into the history of prions

In the 18th and 19th centuries: Exportation of sheep from Spain was observed to coincide with a disease called scrapie. This disease caused the affected animals to "lie down, bite at their feet and legs, rub their backs against posts, fail to thrive, stop feeding, and finally become lame". The disease was also observed to have the long incubation period that is a key characteristic of transmissible spongiform encephalopathy (TSE). Although the cause of scrapie was not known back then, it is probably the first TSE to be recorded.

In 1922: Walter Spielmeyer introduced CJD after the German neurologists Hans Gerhard Creutzfeldt and Alfons Maria Jakob.

In the 1950s: Carleton Gajdusek began research which eventually showed that kuru could be transmitted to chimpanzees by what was possibly a new infectious agent, work for which he eventually won the 1976 Nobel Prize.

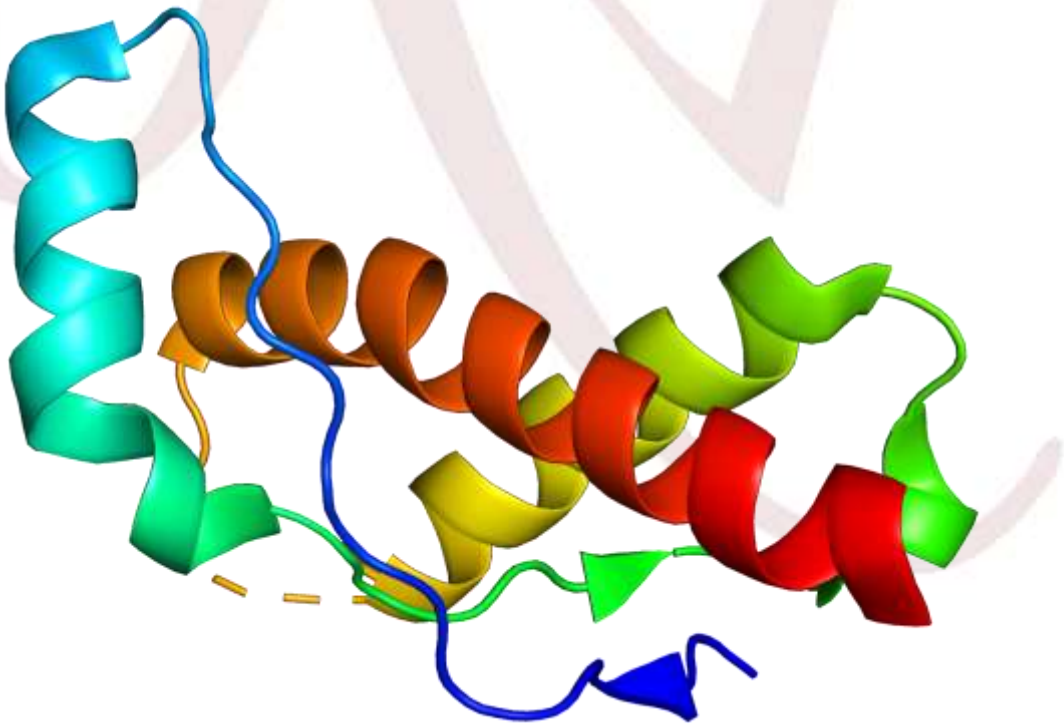
During the 1960s: Two London-based researchers, radiation biologist Tikvah Alper and biophysicist John Stanley Griffith, developed the hypothesis that TSEs are caused by an infectious agent consisting solely of

proteins.

Earlier investigations by E.J. Field into scrapie and kuru had found evidence for the transfer of pathologically inert polysaccharides that only become infectious post-transfer, in the new host. Alper and Griffith wanted to account for the discovery that the mysterious infectious agent causing the diseases scrapie and CJD resisted ionizing radiation.

Francis Crick recognized the potential significance of the Griffith protein-only hypothesis for scrapie propagation in the second edition of his “Central dogma of molecular biology” (1979). While asserting that the flow of sequence information from protein to protein, or from protein to RNA and DNA was "precluded", he noted that Griffith's hypothesis was a potential contradiction (although it was not so promoted by Griffith). The revised hypothesis was later formulated, in part, to accommodate reverse transcription (which both Howard Temin and David Baltimore discovered in 1970).

In 1982: Stanley B. Prusiner of the University of California, San Francisco, announced that his team had purified the hypothetical infectious protein, which did not appear to be present in healthy hosts, though they did not manage to isolate the protein until two years after Prusiner's announcement. The protein was named a prion. Following the discovery of the same protein in different form in uninfected individuals, the specific protein that the prion was composed of was named the prion protein (PrP).



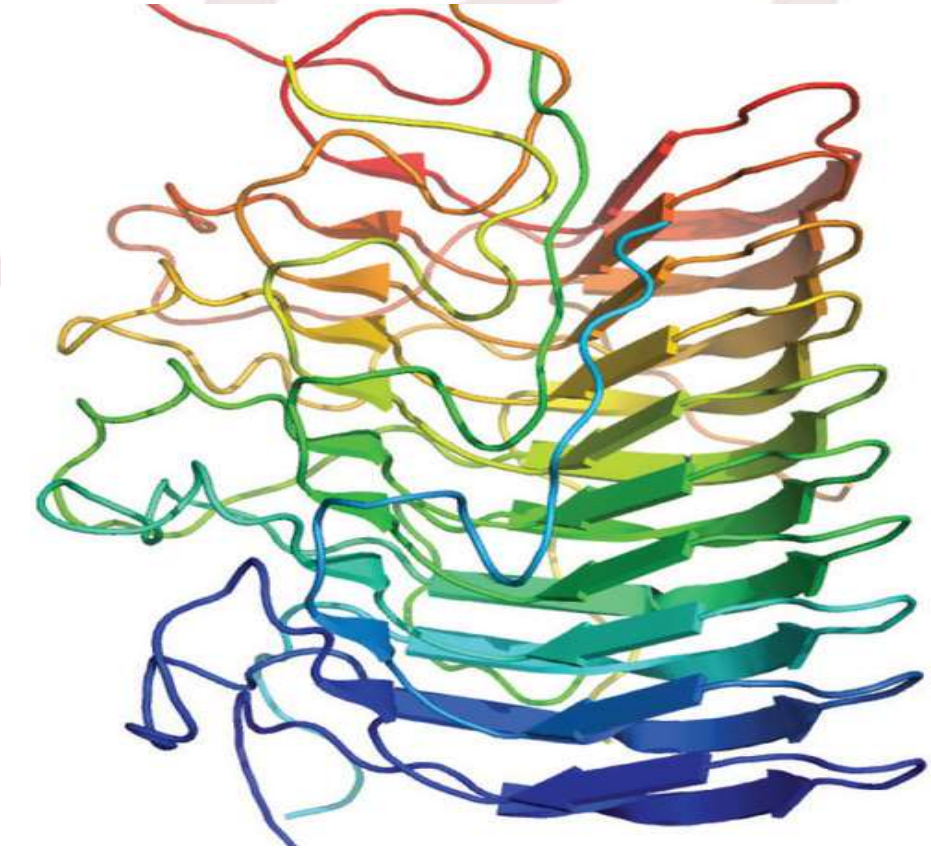
Source: Boghog

Figure 1: Crystallographic structure of the Human Prion Protein 90-231 (based on PDB 6DU9)

What is a prion?

The word is derived from protein and infection, hence prion. It is short for "proteinaceous infectious particle" in reference to its ability to self-propagate and transmit its conformation to other proteins. It was coined in 1982 by the American neurologist and biochemist Stanley B. Prusiner who discovered prions, a class of infectious, self-reproducing pathogens primarily or solely composed of protein - a scientific theory considered by many as a heretical idea when first proposed. For this invention, Prusiner received the 1997 Nobel Prize in Physiology or Medicine.

A prion is a misfolded protein which induces misfolding in normal variants of the same protein, leading to cellular death. Prions are responsible for prion diseases, known as transmissible spongiform encephalopathies (TSE), which are fatal and transmissible neurodegenerative diseases affecting both humans and animals. These proteins can misfold sporadically, due to genetic mutations, or by exposure to an already misfolded protein, leading to an abnormal three-dimensional structure that can propagate misfolding in other proteins. Figure 1 is a cartoon representing the crystallographic structure of the human prion protein 90-231 while the cartoon of Figure 2 depicts the prion protein.



Source: https://medlineplus.gov/images/PX0000E0_PRESENTATION.jpeg

Figure 2: Cartoon depicting the prion protein

Unlike other infectious agents such as viruses, bacteria, and fungi, prions do not contain nucleic acids (DNA or RNA). They are mainly twisted isoforms of the major prion protein (PrP) - a naturally occurring protein with an uncertain function. They are the hypothesized cause of various TSEs, including scrapie in sheep, chronic wasting syndrome (CWS) in deer, bovine spongiform encephalopathy (BSE) in cattle (mad cow disease - MCD), and Creutzfeldt-Jakob disease (CJD) in humans.

Prions are a type of intrinsically disordered proteins that continuously change conformation unless bound to a specific partner, such as another protein. Once a prion binds to another in the same conformation, it stabilizes and can form a "fibril", leading to abnormal protein aggregates called "amyloids" (Figure 3). These amyloids accumulate in infected tissue, causing damage and cell death. The structural stability of prions makes them resistant to denaturation by chemical or physical agents, complicating disposal and containment, and raising concerns about iatrogenic spread through medical instruments.

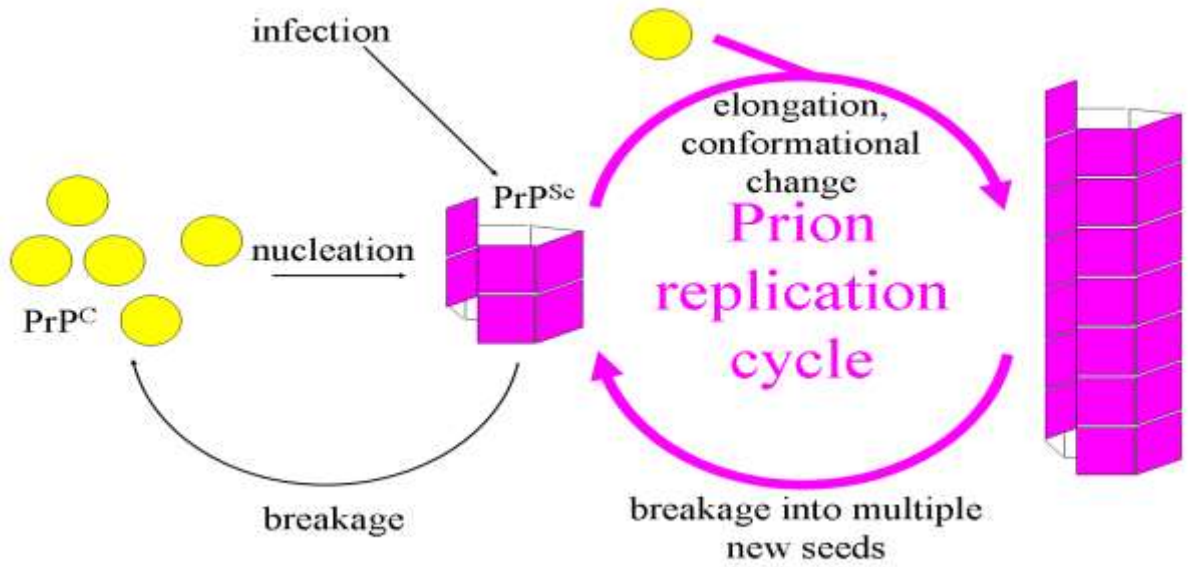


Figure 3: Fibril model of prion propagation

Source: Joannamasel

PrPC = Cellular prion protein; PrPSc = Scrapie prion protein

Prion structure

Prions consist of a misfolded form of the major prion protein (PrP), a protein that is a natural part of the bodies of humans and other animals. The PrP found in infectious prions 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 PrPC, while the infectious form is called PrPSc – (C refers to 'cellular' PrP, while Sc refers to 'scrapie', the prototypic prion disease, occurring in sheep). PrP can also be induced to fold into other more-or-less well-defined isoforms in vitro; although their relationships to the form(s) that are pathogenic in vivo are often unclear, high-resolution structural analyses have begun to reveal structural features that correlate with prion infectivity. The term "PrPres" may refer either to protease-resistant forms of PrPSc.

Cellular prion protein PrP^{C}

PrP^{C} is a normal protein found on the membranes of cells, including several blood components of which platelets constitute the largest reservoir in humans. It has 209 amino acids (in humans), one disulfide bond, a molecular mass of 35–36 kDa, and a mainly alpha-helical structure (see Figure 1). 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. It has a complex function, which continues to be investigated.

PrP^{C} binds copper ions with high affinity. This property is supposed to play a role in PrPC's anti-oxidatve properties via reversible oxidation. Moreover, studies have suggested that, in vivo, due to PrP^{C}'s low selectivity to metallic substrates, the protein's anti oxidative function is impaired when in contact with metals other than copper.

PrP^{C} is readily digested by proteinase K and can be liberated from the cell surface. It plays an important role in cell-cell adhesion and intracellular signaling in vivo. and may therefore be involved in cell-cell communication in the brain.

Scrapie prion protein PrP^{Sc}

The infectious isoform of PrP, known as PrP^{Sc} can convert normal PrPC proteins into the infectious isoform by changing their conformation or shape; this, in turn, alters the way the proteins interconnect. PrPSc always causes prion disease. Several highly infectious, brain-derived PrP^{Sc} structures have been discovered by cryo-electron microscopy. Another brain-derived fibril structure isolated from humans with Gerstmann-Straussler-Scheinker syndrome (GSSS) has also been determined.

Protease-resistant prion protein PrP^{res}

The term "PrP^{res}" may refer either to protease-resistant forms of PrP^{Sc}, which is isolated from infectious tissue and associated with the TSE agent, or to other protease-resistant forms of PrP that, for example, might be generated in vitro. Accordingly, unlike PrPSc, PrPres may not necessarily be infectious.

Protease-resistant PrP^{Sc}-like protein (PrP^{res}) is the name given to any isoform of PrP^{c} which is structurally altered and converted into a misfolded proteinase K-resistant form. To model conversion of PrP^{C} to PrP^{Sc} *in vitro*, *Kocisko et al.* showed that PrP^{Sc} could cause PrP^{C} to convert to PrPres under cell-free conditions. Further, *Soto et al.* demonstrated sustained amplification of PrP^{res} and prion infectivity by a procedure involving

cyclic amplification of protein misfolding.

Genetic susceptibility

The majority of human prion diseases are classified as sporadic Creutzfeldt–Jakob disease (sCJD). Genetic research has identified an association between susceptibility to sCJD and a polymorphism at codon 129 in the PRNP gene, which encodes the prion protein (PrP). A homozygous methionine/methionine (MM) genotype at this position has been shown to significantly increase the risk of developing sCJD when compared to a heterozygous methionine/valine (MV) genotype. Analysis of multiple studies has shown that individuals with the MM genotype are approximately five times more likely to develop sCJD than those with the MV genotype.

Normal functions of the prion protein

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 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, RIP1, and RIP3 are prion-like proteins found in other parts of the body. They also polymerize 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

In 2005, a review of evidence available suggested that PrP may have a normal function in the maintenance of long-term memory. Also, a 2004 study found that mice lacking genes for normal cellular PrP protein show altered hippocampal long-term potentiation. A recent study that also suggests why this might be the case, found that the 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.

PrP and innate immunity

There is some evidence that PrP may play a role in innate immunity, as the expression of PRNP, the PrP gene, is upregulated in many viral infections and PrP has antiviral properties against many viruses, including HIV.

Models of prion replication and implications for drug design

There are essentially two models (hypotheses) that try to explain how prions replicate in a protein-like manner.

Heterodimer model

This model assumes that a single PrPSc molecule binds to a single PrPC molecule and catalyzes its conversion into PrPSc. The two PrPSc molecules then come apart and can go on to convert more PrPC. However, a model of prion replication must explain both how prions propagate, and why their spontaneous appearance is so rare. Manfred Eigen showed that the heterodimer model requires PrPSc to be an extraordinarily effective

catalyst, increasing the rate of the conversion reaction by a factor of around 1015. This problem does not arise if PrPSc exists only in aggregated forms such as amyloid, where cooperativity may act as a barrier to spontaneous conversion. What is more, despite considerable effort, infectious monomeric PrPSc has never been isolated.

Fibril model

An alternative model assumes that PrP^{Sc} exists only as fibrils, and that fibril ends bind PrP^{C} and convert it into PrP^{Sc}. If this were all, then the quantity of prions would increase linearly, forming ever longer fibrils. But exponential growth of both PrP^{Sc} and the quantity of infectious particles is observed during prion disease. This can be explained by considering fibril breakage. A mathematical solution for the exponential growth rate resulting from the combination of fibril growth and fibril breakage has been found. The exponential growth rate depends largely on the square root of the PrP^{C} concentration. The incubation period is determined by the exponential growth rate, and *in vivo* data on prion diseases in transgenic mice match this prediction. The same square root dependence is also seen in vitro in experiments with a variety of different amyloid proteins.

Implications for drug design

The mechanism of prion replication has implications for designing drugs. Since the incubation period of prion diseases is so long, an effective drug does not need to eliminate all prions but simply needs to slow down the rate of exponential growth. Models predict that the most effective way to achieve this, using a drug with the lowest possible dose, is to find a drug that binds to fibril ends and blocks them from growing any further.

Researchers at Dartmouth College discovered that endogenous host cofactor molecules such as the phospholipid molecule (e.g. phosphatidylethanolamine) and polyanions (e.g. single stranded RNA molecules) are necessary to form PrP^{Sc} molecules with high levels of specific infectivity *in vitro*, whereas protein-only PrP^{Sc} molecules appear to lack significant levels of biological infectivity.

Prion transmission

As stated in an earlier section, it has been recognized that prion diseases can arise in four different ways:

- Acquired,
- Familial,
- Sporadic. and
- Iatrophic.

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 PrPC to PrPSc by bringing a molecule of each of the two together into a complex.

There are three (possibly four) transmission paths, including:

- **Ingestion:** 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 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.

- **Environment:** In 2015, researchers at The University of Texas, Health Science Center in Houston found that plants can be a vector for

prions. When researchers fed hamsters grass that grew on ground where a deer that died with chronic wasting disease (CWD) was buried, the hamsters became ill with CWD. This result suggests that prions can bind to plants, which then take them up into the leaf and stem structure, where they can be eaten by herbivores, thus completing the cycle. It is thus possible that there is a progressively accumulating number of prions in the environment.

- **Airborne transmission:** Although it was initially reported in January 2011 that researchers had discovered prions spreading through airborne transmission on aerosol particles in an animal testing experiment focusing on scrapie infection in laboratory mice, this report was retracted in 2024.

- **Laboratory transmission:** Preliminary evidence supporting the notion that prions can be transmitted through use of urine-derived human menopausal gonadotropin administered for the treatment of infertility was published in 2011.

Prion degradation

Prions can degrade through two processes:

Degradation resistance in nature

Overwhelming evidence shows that prions resist degradation and persist in the environment for years. Also, proteases do not degrade them. Experimental evidence shows that unbound prions degrade over time, while soil-bound prions remain at stable or increasing levels, suggesting that prions likely accumulate in the environment. One 2015 study by US scientists found that repeated drying and wetting may render soil-bound prions less infectious, although this was dependent on the soil type to which they were bound.

Degradation by living beings

More recent studies suggest that scrapie prions can be degraded by diverse cellular machinery of the affected animal cell. In an infected cell, extracellular lysosomal PrPSc does not tend to accumulate and is rapidly cleared by the lysosome via the endosome. The intracellular portion is harder to clear and tends to build up. The ubiquitin proteosome system (UPS) appears to be able to degrade small enough aggregates.

Autophagy promotion and inhibition

Autophagy plays a bigger role by accepting PrPSc from the ER lumen and degrading it. Altogether, these mechanisms allow the cell to delay its death from being overwhelmed by misfolded proteins. Inhibition of autophagy accelerates prion accumulation whereas encouragement of autophagy promotes prion clearance. Some autophagy-promoting compounds have shown promise in animal models by delaying disease onset and death.

Treatments

There are no effective treatments for prion diseases. Clinical trials in humans have not met with success and have been hampered by the rarity of prion diseases. Although some potential treatments have shown promise in the laboratory, none have been effective once the disease has commenced.

Case of other diseases

Prion-like domains have been found in a variety of other mammalian proteins. Some of these proteins have been implicated in the ontogeny of age-related neurodegenerative disorders such as amyotrophic lateral sclerosis (ALS), frontotemporal degeneration with ubiquitin-positive inclusions (FTLD-U). Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington's disease (HD). They are also implicated in some forms of systemic amyloidosis including AA

amyloidosis that develops in humans and animals with inflammatory and infectious diseases such as tuberculosis, Crohn's disease (CD), rheumatoid arthritis (RA), and HIV/AIDS. AA amyloidosis, like prion disease, may be transmissible. This has given rise to the 'prion paradigm', where otherwise harmless proteins can be converted to a pathogenic form by a small number of misfolded, nucleating proteins.

Bioinformatic screens have predicted that over 250 human proteins contain prion-like domains (PrLD). These domains are hypothesized to have the same transmissible amyloidogenic properties of PrP and known fungal proteins. As in yeast, proteins involved in gene expression and RNA binding seem to be particularly enriched in PrLD's, compared to other classes of protein. In particular, 29 of the known 210 proteins with an RNA recognition motif also have a putative prion domain. Meanwhile, several of these RNA-binding proteins have been independently identified as pathogenic in cases of ALS, FTLD-U, AD, and HD.

Links to and roles in other neurodegenerative diseases

All known prion diseases in mammals affect the structure of the brain or other neural tissues. These diseases are progressive, have no known effective treatment, and are invariably fatal. The pathogenicity of prions and proteins with prion-like domains is hypothesized to arise from their self-templating ability and the resulting exponential growth of amyloid fibrils. The presence of amyloid fibrils in patients with degenerative diseases has been well documented. These amyloid fibrils are seen as the result of pathogenic proteins that self-propagate and form highly stable, non-functional aggregates. While this does not necessarily imply a causal relationship between amyloid and degenerative diseases, the toxicity of certain amyloid forms and the overproduction of amyloid in familial cases of degenerative disorders supports the idea that amyloid formation is generally toxic.

Specifically, aggregation of TAR (transactive response)-DNA binding protein-43 (TDP-43), an RNA-binding protein, has been found in ALS/MND patients, and mutations in the genes coding for these proteins have been identified in familial cases of motor neuron diseases such as ALS (ALS/MND). These mutations promote the misfolding of the proteins into a prion-like conformation. The misfolded form of TDP-43 forms cytoplasmic inclusions in affected neurons and is found depleted in the nucleus. In addition to ALS/MND and FTLD-U, TDP-43 pathology is a feature of many cases of AD, PD, and HD. The misfolding of TDP-43 is largely directed by its prion-like domain. This domain is inherently prone to misfolding, while pathological mutations in TDP-43 have been found to increase this propensity to misfold, explaining the presence of these mutations in familial cases of ALS/MND. The prion-like domain of TDP-43 has been shown to be both necessary and sufficient for protein misfolding and aggregation.

Similarly, pathogenic mutations have been identified in the prion-like domains of heterogeneous nuclear riboproteins hnRNPA2B1 and hnRNPA1 in familial cases of muscle, brain, bone and motor neuron degeneration. The wild-type form of all of these proteins shows a tendency to self-assemble into amyloid fibrils, while the pathogenic mutations exacerbate this behavior and lead to excess accumulation.

Conclusions and take-aways

- A prion is a misfolded protein which induces misfolding in normal variants of the same protein, leading to cellular death. Prions are responsible for prion diseases known as transmissible spongiform encephalopathies, which are fatal and transmissible neurodegenerative diseases affecting both

humans and animals.

- Prion proteins can misfold sporadically, due to genetic mutations, or by exposure to an already misfolded protein, leading to an abnormal three-dimensional structure that can propagate misfolding in other proteins. They are mainly twisted isoforms of the major prion protein (PrP) - a naturally occurring protein with an uncertain function.

- Unlike other infectious agents such as viruses, bacteria, and fungi, prions do not contain nucleic acids (DNA or RNA).

- Prions are linked to other neurodegenerative diseases like Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis, which are sometimes referred to as prion-like diseases.

- Prions consist of a misfolded form of the major prion protein, a protein that is a natural part of the bodies of humans and other animals. Infectious prions have a different structure and are resistant to proteases.

- The physiological function of the prion protein remains poorly understood. While data from in vitro experiments suggest many dissimilar roles, mice studies have provided only limited information.

- The first hypothesis that tried to explain how prions replicate in a protein-only manner was the heterodimer model. A model of prion replication must explain both how prions propagate, and why their spontaneous appearance is so rare.

- The mechanism of prion replication has implications for designing drugs. Since the incubation period of prion diseases is so long, an effective drug does not need to eliminate all prions but simply needs to slow down the rate of exponential growth. Models predict that the most effective way to achieve this, using a drug with the lowest possible dose, is to find a drug that binds to fibril ends and blocks them from growing any further.

- Prions cause neurodegenerative diseases by aggregating extracellularly within the central nervous system to form plaques known as amyloids, which disrupt the normal tissue structure. This disruption is characterized by "holes" in the tissue with resultant spongy architecture due to the vacuole formation in the neurons. Other histological changes include astrogliosis and the absence of an inflammatory reaction.

- While the incubation period for prion diseases is relatively long (5 to 20 years), once symptoms appear the disease progresses rapidly, leading to brain damage and death.

- Neurodegenerative symptoms can include convulsions, dementia, ataxia (balance and coordination dysfunction), and behavioral or personality changes.

- All known prion diseases are untreatable and fatal.

- There are no effective treatments for prion diseases. Clinical trials in humans have not met with success and have been hampered by the rarity of prion diseases. Although some potential treatments have shown promise in the laboratory, none have been effective once the disease has commenced.

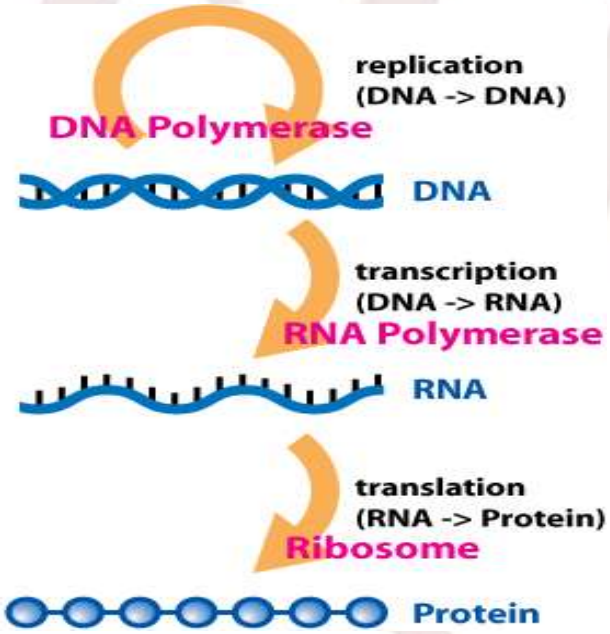
- The Sidebar revisits the central dogma of

molecular biology

Sidebar – The central dogma of molecular biology revisited

The central dogma of molecular biology describes the flow of genetic information within a biological system (a cell), primarily from DNA to RNA to protein. It is often stated as "DNA makes RNA, and RNA makes protein", although this is not its original meaning. Information here means the precise determination of sequence, either of bases in the nucleic acid or of amino acid residues in the protein.

The central dogma was first stated by Francis Crick in 1957, then published in 1958 and re-stated in a Nature paper published in 1970: This one-way flow ensures the accurate synthesis of proteins, which are essential for cellular function. The dogma also states that once "information" has passed into protein; it cannot get out again. In more detail, the transfer of information from nucleic acid to nucleic acid, or from nucleic acid to protein may be possible, but transfer from protein to protein, or from protein to nucleic acid is impossible (see Figure 4).



Source: Dhorspool

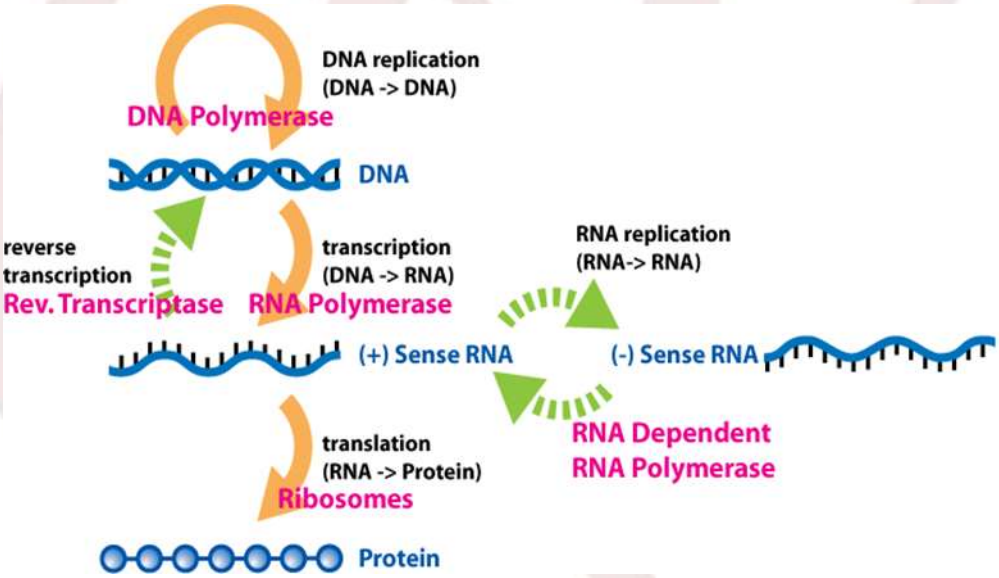
"The central dogma of molecular biology deals with the detailed residue-by-residue transfer of sequential information. It states that such information cannot be transferred back from protein to either protein or nucleic acid."

Figure 4 - An overview of the (basic) central dogma of molecular biochemistry with all enzymes labeled

The transfers of information from one molecule to another are faithful, deterministic transfers wherein one biopolymer's sequence is used as a template for the construction of another biopolymer with a sequence that is entirely dependent on the original biopolymer's sequence. When DNA is transcribed to RNA, its

complement is paired to it. DNA codes are transferred to RNA codes in a complementary fashion. The encoding of proteins is done in groups of three, known as codons. The standard codon table applies for humans from RNA to DNA (the reverse of normal transcription). It is the process by which genetic information from RNA gets transcribed into new DNA.

A second version of the central dogma is popular but incorrect. This is the simplistic DNA → RNA → protein pathway published by James Watson in the first edition of The Molecular Biology of the Gene (1965). Watson's version differs from Crick's because Watson describes a two-step (DNA → RNA and RNA → protein) process as the central dogma (Figure 5). While the dogma as originally stated by Crick remains valid today, Watson's version does not.



Source: Dhorspool

Figure 5 - Unusual flows of information highlighted in green

Activities unrelated to the central dogma

As just stated, the central dogma of molecular biology states that, once sequential information has passed from nucleic acid to protein, it cannot flow back from protein to nucleic acid. However, the following activities may conflict with the central dogma:

- **Post-translational modification:** After protein amino acid sequences have been translated from nucleic acid chains, they can be edited by appropriate enzymes. This is a

form of protein affecting protein sequence not protein transferring information to nucleic acid.

- **Non-ribosomal peptide synthesis:** Some proteins are synthesized by non-ribosomal peptide synthetases, which can be big protein complexes, each specializing in synthesizing only one type of peptide. Non-ribosomal peptides often have cyclic and/or branched structures and can contain non-proteinogenic amino acids - both factors differentiate them from ribosome synthesized proteins. Examples of non-ribosomal peptides are some of the antibiotics.

- **Inteins:** An intein is a "parasitic" segment of a protein that can excise itself from the chain of amino acids as they emerge from the ribosome and rejoin the remaining portions with a peptide bond in such a manner that the main protein "backbone" does not fall apart. This is a case of a protein changing its own primary sequence from the sequence originally encoded by the DNA of a gene. Additionally, most inteins contain a homing endonuclease (HEN) domain which can find a copy of the parent gene that does not include the intein nucleotide sequence. On contact with the intein-free copy, the HEN domain initiates the DNA double-stranded break repair mechanism. This process causes the intein sequence to be copied from the original source gene to the intein-free gene. This is an example of protein directly editing DNA sequence, as well as increasing the sequence's heritable propagation.

- **Prions:** Prions are proteins of particular amino acid sequences in particular conformations. They propagate themselves in host cells by making conformational changes in other molecules of protein with the same amino acid sequence, but with a different conformation that is functionally important or detrimental to the organism. Once the protein has been trans-conformed to the prion folding, it changes function. In turn, it can convey information into new cells and reconfigure more functional molecules of that sequence into the alternate prion form. In some types of prions in fungi, this change is continuous and direct; the information flow is Protein → Protein. Some scientists (Alain E. Bussard, Eugene Kroonin, and others) have argued that prion-mediated inheritance violates the central dogma of molecular biology. However, Rosalind Ridley has written in Molecular Pathology of the Prions (2001) that:

"The prion hypothesis is not heretical to the central dogma of molecular biology—that the information necessary to manufacture proteins is encoded in the nucleotide sequence of nucleic acid—because it does not claim that proteins replicate. Rather, it claims that there is a source of information within protein molecules that contributes to their biological function, and that this information can be passed on to other molecules."

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