453e Prion Diseases

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Prions are proteins that adopt an alternative conformation, which becomes self-propagating. Some prions cause degeneration of the central nervous system (CNS). Once relegated to causing a group of rare disorders of the CNS such as Creutzfeldt-Jakob disease (CJD), prions—as mounting evidence shows—also appear to play a key role in more common illnesses such as Alzheimer's disease (AD) and Parkinson's disease (PD). While CJD is caused by the accumulation of PrP^{Sc}, increasing data argue that Aβ prions cause AD, α-synuclein prions cause PD, and tau prions cause the frontotemporal dementias (FTDs). In this chapter, we confine our discussion to CJD, which typically presents with a rapidly progressive dementia as well as motor abnormalities. The illness is relentlessly progressive and generally causes death within 9 months of onset. Most CJD patients are between 50 and 75 years of age; however, patients as young as 17 and as old as 83 have been recorded.

CJD is one malady in a group of disorders caused by prions composed of the prion protein (PrP). PrP prions reproduce by binding to the normal, *c*ellular isoform of the *p*rion *p*rotein (PrP^{C}) and stimulating conversion of PrP^{C} into the disease-*c*ausing isoform PrP^{Sc}. PrP^{C} is rich in α-helix and has little β-structure, whereas PrP^{Sc} has less α-helix and a high amount of β-structure (Fig. 453e-1). This α-to-β structural transition in PrP is the fundamental event underlying this group of prion diseases (Table 453e-1).

Four new concepts have emerged from studies of prions: (1) Prions are the only known transmissible pathogens that are devoid of nucleic acid; all other infectious agents possess genomes composed of either RNA or DNA that direct the synthesis of their progeny. (2) Prion diseases may be manifest as infectious, genetic, and sporadic disorders; no other group of illnesses with a single etiology presents with such a wide spectrum of clinical manifestations. (3) Prion diseases result from the accumulation of PrP^{Sc}, the conformation of which differs substantially from that of its precursor, PrP^{C}. (4) Distinct strains of prions exhibit different biologic properties, which are epigenetically inherited. In other words, PrP^{Sc} can exist in a variety of different conformations, many of which seem to specify particular disease phenotypes.

How a specific conformation of a PrP^{Sc} molecule is imparted to PrP^{C} during prion replication to produce nascent PrP^{Sc} with the same conformation is unknown. Additionally, it is unclear what factors determine where in the CNS a particular PrP^{Sc} molecule will be deposited.

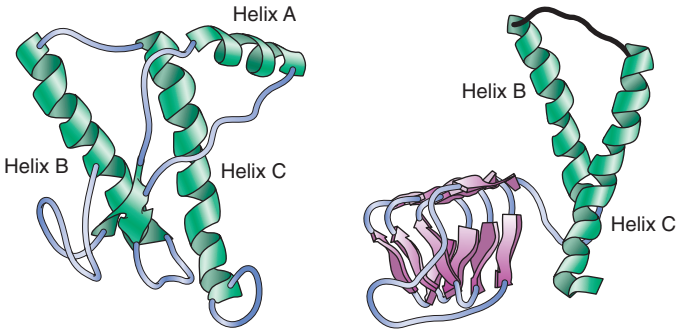

FIGURE 453e-1 Structures of prion proteins. ***A.*** NMR structure of Syrian hamster recombinant (rec) PrP(90–231). Presumably, the structure of the α-helical form of recPrP(90–231) resembles that of PrP^{C}. recPrP(90–231) is viewed from the interface where PrP^{Sc} is thought to bind to PrP^{C}. Shown are: α-helices A (residues 144–157), B (172–193), and C (200–227). Flat ribbons depict β-strands S1 (129–131) and S2 (161–163). ***B.*** Structural model of PrP^{Sc}. The 90–160 region has been modeled onto a β-helical architecture while the COOH terminal helices B and C are preserved as in PrP^{C}.

TABLE 453e-1 GLOSSARY OF PRION TERMINOLOGY

Prion	*Pro*teinaceous *in*fectious particle that lacks nucleic acid. Prions are composed entirely of alternatively folded proteins that undergo self-propagation. Distinct strains of prions exhibit different biologic properties, which are epigenetically heritable. PrP prions cause scrapie in sheep and goats, mad cow disease, and related neurodegenerative diseases of humans such as Creutzfeldt-Jakob disease (CJD).
PrP^{Sc}	Disease-causing isoform of the prion protein. This protein is the only identifiable macromolecule in purified preparations of scrapie prions.
PrP^{C}	Cellular isoform of the prion protein. PrP^{C} is the precursor of PrP^{Sc}.
PrP 27-30	A fragment of PrP^{Sc}, generated by truncation of the NH_2-terminus by limited digestion with proteinase K. PrP 27-30 retains prion infectivity and polymerizes into amyloid.
PRNP	PrP gene located on human chromosome 20.
Prion rod	An aggregate of prions composed largely of PrP 27-30 molecules. Created by detergent extraction and limited proteolysis of PrP^{Sc}. Morphologically and histochemically indistinguishable from many amyloids.
PrP amyloid	Amyloid containing PrP in the brains of animals or humans with prion disease; often accumulates as plaques.

SPECTRUM OF PRION DISEASES

The sporadic form of CJD is the most common prion disorder in humans. Sporadic CJD (sCJD) accounts for ~85% of all cases of human PrP prion disease, whereas inherited prion diseases account for 10–15% of all cases (Table 453e-2). Familial CJD (fCJD), Gerstmann-Sträussler-Scheinker (GSS) disease, and fatal familial insomnia (FFI) are all dominantly inherited prion diseases that are caused by mutations in the PrP gene.

Although infectious PrP prion diseases account for <1% of all cases and infection does not seem to play an important role in the natural history of these illnesses, the transmissibility of

TABLE 453e-2 THE PrP PRION DISEASES

Disease	Host	Mechanism of Pathogenesis
Human		
Kuru	Fore people	Infection through ritualistic cannibalism
iCJD	Humans	Infection from prion-contaminated hGH, dura mater grafts, etc.
vCJD	Humans	Infection from bovine prions
fCJD	Humans	Germline mutations in *PRNP*
GSS	Humans	Germline mutations in *PRNP*
FFI	Humans	Germline mutation in *PRNP* (D178N, M129)
sCJD	Humans	Somatic mutation or spontaneous conversion of PrP^{C} into PrP^{Sc}?
sFI	Humans	Somatic mutation or spontaneous conversion of PrP^{C} into PrP^{Sc}?
Animal		
Scrapie	Sheep, goats	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 beef
Exotic ungulate encephalopathy	Greater kudu, nyala, or oryx	Infection with prion-contaminated MBM

Abbreviations: BSE, bovine spongiform encephalopathy; CJD, Creutzfeldt-Jakob disease; CWD, chronic wasting disease; fCJD, familial Creutzfeldt-Jakob disease; FFI, fatal familial insomnia; FSE, feline spongiform encephalopathy; GSS, Gerstmann-Sträussler-Scheinker disease; hGH, human growth hormone; iCJD, iatrogenic Creutzfeldt-Jakob disease; MBM, meat and bone meal; sCJD, sporadic Creutzfeldt-Jakob disease; sFI, sporadic fatal insomnia; TME, transmissible mink encephalopathy; vCJD, variant Creutzfeldt-Jakob disease.