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"PRIONS" – A BASIC REVIEW

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Abstract

Novel infectious particles, termed prions, composed of a single protein are causative agents of a group of diseases that produce lethal decline of motor function. Prion diseases are among the most intriguing illnesses. Prion diseases are fatal neurodegenerative disorders that can arise spontaneously, be inherited, or be acquired by infection in mammals. This article gives a basic over view of prion proteins and prion diseases.

Introduction

The term prion, (pronounced pree-on and derived from proteinaceous infectious particle') refers to a small infectious agent that consists of protein but lacks nucleic acid (1). The unusual properties of the infectious agent became the focus of attention beginning in the 1960s, and in the early 1980s Stanley Prusiner, building upon earlier suggestions (2,3), proposed the prion hypothesis (4). This stated that the infectious agent in human and animal spongiform encephalopathies was composed exclusively of a single kind of protein molecule designated PrPSc without any encoding nucleic acid (4). Prions are characterized by extreme resistance to conventional inactivation procedures including irradiation, boiling, dry heat and chemicals (formalin, Betapropiolactone and alcohols). They are inactivated by 1N Sodium Hydroxide (NaOH); 4.0 Guanidine hydrochloride or isocyanate; sodium hypochloride (2% free chlorine concentration); steam autoclaving at 132° C for 4.5 hrs and incineration (5).

Prion protein is expressed constitutively in many cell-types and is the product of a single exon. It exists as a membrane-bound monomer of 231 amino acids. The N-terminal of the protein carries a signal sequence of 23 amino acids while the C-terminal contains a signal sequence for a glycosylphosphatidyl inositol (GPI) anchor. Glycosylation sites are also present near the C-terminal and the protein may exist in unglycosylated, mono-glycosylated and diglycosylated form (6).

Structural and biochemical investigations have revealed the presence of high α helical content and high proteolytic susceptibility of the cellular form PrPc, whereas the scrapie form, PrP^{sc}, shows high β sheet content coupled with high protease resistance (7). The two isoforms, PrP^{C} and PrP^{Sc}, only differ in conformation and have the same primary amino acid sequence [8]. This, along with the absence of nucleic acid in the prion protein, suggests that the conversion occurs post-translationally [8]. While PrP^{C} is composed of 42% α-helix and only 3% β-sheet, PrP^{Sc} is composed of 30% α-helix and 43% β-sheet [8]. Various models have suggested that PrP^{C} converts to its pathogenic isoform when the region corresponding to the residues 108-144 fold into β-sheets [8]. Because of these structural differences, the two isoforms have different biochemical characteristics. PrP^{C} is very soluble in detergents and easily digested by proteases while the PrP^{Sc} is insoluble in detergents and resistant to protease digestion [8].

Comparison of PrP^{c} and PrP^{sc} (19)

Comparison of PrP^{c} and PrP^{sc} Properties	PrP^{c}	PrP^{sc}
Isoform	Normal	Pathogenic
Protease resistance	No	Stable core containing residue 90-231
Location in or on cells	Plasma membrane	Cytoplasmic vesicles
Solubility	Soluble	Insoluble
PK-sensitivity	Sensitive	Partially resistant
Structure	Extended	Globular
α-Helices	45%	30%

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β-Sheets	3%	45%
Glycoforms	Mixture of un-, mono and di-glycosylated forms	Mixture of un-, mono and di-glycosylated forms
Infectivity	No	Yes
Turnover	Hours	Days
Sedimentation properties	Consistent with monomeric species	Multimeric aggregated species

PrP denotes prion protein and PrP^{sc} the scrapie isoform of PrP^{c}

Prion diseases: Basic overview

These are slow, progressive, neurodegenerative diseases. Prion diseases are rare & occur world wide (9). Prion diseases exist in infectious, sporadic, and genetic forms. The infectious prion diseases are speculated to result from a spontaneous conversion of endogenous PrP^{C} to PrP^{Sc} or following the introduction of PrP^{Sc} in the body [10].

Table 1: Prions diseases (11)

(sporadic, inherited and transmissible forms)
Human:
Kuru
Creutzfeldt-Jakob disease (CJD)
Variant CJD (v CJD)
Gerstmann-straussler-scheinker
(GSS syndrome)
Fatal familial insomnia (FFI)
Animal:
Scrapie (sheep and goats)
Transmissible mink encephalopathy
Bovine spongiform encephalopathy
(BSE, mad cow disease)
Chronic wasting disease
(mule, deer and elk)

The most common type of prion disease in humans is the Creutzfeldt-Jakob disease (12). The BSE outbreak captured the attention of many people when almost 200,000 cattle died (13). Scrapie prion protein can be introduced into the body through consumption of infected cow meat as in the case of Bovine Spongiform Encephalopathy or through the reuse of surgical instruments that are contaminated with infectious prions (infection through this manner is known as iatrogenic CJD) [14, 15]. The etiology of sporadic prion diseases is unknown although it is thought to be the result of randomly misfolding of PrP^{C} to PrP^{Sc}, which allows for further conversion of normal prion protein to PrP^{Sc} [16]. Prion diseases induce death when the PrP^{Sc} accumulates in the brain, resulting in neuronal death and the creation of microscopic holes, known as vacuoles, in the brain [17]. vCJD has been effecting young adults less then 40 years of age , manifesting predominantly as psychiatric disorders (1).

Natural Transmission (18)

Disease	Mode Of Transmission
Infectious	
Scrapie	Exposure of lambs to infected sheep
Chronic wasting disease	Pasture contamination
Kuru	Endocannibalism
Transmissible mink encephalopathy	Feed and possibly cannibalism
Bovine spongiform encephalopathy	Meat-and-bone meal fed to calves
Variant CJD	Probable consumption of infected cattle
Genetic	
Familial CJD	Mutations in PRNP

Unknown	
Sporadic CJD	Unknown

Conclusion

Prions are elements that impart and propagate variability through multiple conformers of a normal cellular protein. A more in – depth review and research is in need to study prion proteins in detail.

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