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Note: This paper has been modified to better illustrate the desired format for student papers.

Prion Disease
(*Mad Cow Disease*)

Abstract

Prion disease is a group of transmissible disorders fatally affecting the brains of humans and certain animas. Proteinaceous material likely acts as infectious agents similar to a virus. The lack of nucleic acid in these proteins creates significant controversy in the field of medicine and modern biology. A direct connection has yet to be demonstrated between a prion and transmission of disease. Several of the leading hypotheses involving the infectious nature of some proteins and its relationship to the "Mad Cow Epidemic" are explored. Despite a proven link there is far too much evidence to ignore the health risk.

Introduction

Prion disease

Prion diseases, also known as spongiform encephalopathies, are a group of transmissible disorders that affect the brains of humans and animals and are invariably fatal. The nature of the pathogenic agent is unique. In contrast to all other known infectious agents (for example, viruses, bacteria, yeast), which contain nucleicacids as information carriers, the infectious prion pathogen seems to lack this component. The prevailing view is that the molecule responsible for the transmission of the spongiform encephalopathies is the structural isoform of a protein, named prion protein (the term prion is a skewed acronym for proteinaceous infectious agent). The identification of an infectious agent that apparently does

not require a nucleic acid for replication presents a fascinating puzzle in modern biology and medicine.

Main Body

Molecular basis

A hallmark of spongiform encephalopathies is the cerebral accumulation of an abnormal prion protein which is resistant to proteolytic enzymes. This aberrant protein is derived from a cellular (nonpathogenic) form of prion protein that is normally present. The two forms of the protein have identical sequences of amino acids (the building blocks of proteins) but appear to have markedly different physicochemical properties. While the normally occurring prion protein is soluble in water and easily degradable by proteolytic enzymes, the abnormal prion protein forms insoluble aggregates resistant to enzymatic proteolysis. Furthermore, recent structural studies revealed profound differences in the conformation (three-dimensional shape) of the two protein isoforms: the normal cellular prion protein contains three helices and only two very short strands; the proteolytic enzyme-resistant prion protein has a high content of sheet structure. According to the protein-only hypothesis of prion disease, the sole causative agent is the pathogenic form of the protein (proteolytic enzyme-resistant), and the central event in the transmission of the disease is the conversion of the benign conformation of normally occurring prion protein into the pathological conformation.

In view of the pathogenic mechanism, prion diseases may be classified as conformational diseases. Other examples of this diverse group of otherwise-unrelated disorders, which appear to arise from abnormal folding of an underlying protein (that is different in each case), include Alzheimer's disease, various forms of systemic amyloidosis,

Huntington's disease, sickle cell anemia, and cystic fibrosis. However, the unique feature of prion diseases is that they are transmissible.

The mechanism of prion disease propagation is not fully understood. However, rapidly accumulating data support the protein-only hypothesis. The key evidence in this respect was obtained from experiments showing that upon infection with the aberrant prion protein-containing material, transgenic mice devoid of normal prion protein are completely protected against the pathogen,[3] whereas the wild-type animals (for example, those containing the normal prion protein gene) develop disease;[5] the abnormal prion protein expressed by animals challenged with exogenous prion particles reproduces the physicochemical characteristics of the injected proteolytic enzyme-resistant prion protein.[3,5] Two distinct models have been proposed for the molecular mechanism of the standard-to-aberrant prion protein conversion (fig-1.). The template-assisted refolding model postulates that, because of a very high energy barrier, the spontaneous conversion of normal prion protein into a resistant form is very unlikely.[3, 2, 5] However, in the presence of the abnormal protein (either acquired by infection or formed spontaneously), the two isoforms interact, generating a proteolytic enzyme-resistant/nonresistant heterodimer.[4] The proteolytic enzyme-resistant prion protein in this complex would act as a template, inducing (or catalyzing) the conversion of normal prion protein to the resistant conformation.[2, 5] The newly formed protein resistant to proteolysis could, in turn, engage in a similar interaction with another responsive (normal) prion protein molecule, resulting in an exponential conversion cascade. According to the seeding model, the infectious unit is not the abnormal prion protein monomer but only a prion protein aggregate, and the conversion occurs as a nucleation-dependent polymerization process. Thus, in the absence of preexisting aberrant prion protein aggregate, the transition between normal and abnormal prion protein is reversible, but the proteolytic enzyme-resistant monomer is less stable than the prion protein susceptible to proteolysis. Stabilization of the

resistant conformation occurs only in the presence of a protein oligomer which acts as a template; the monomeric protein can successively deposit onto this template, adopting its conformational structure.[1, 3, 4, 5]

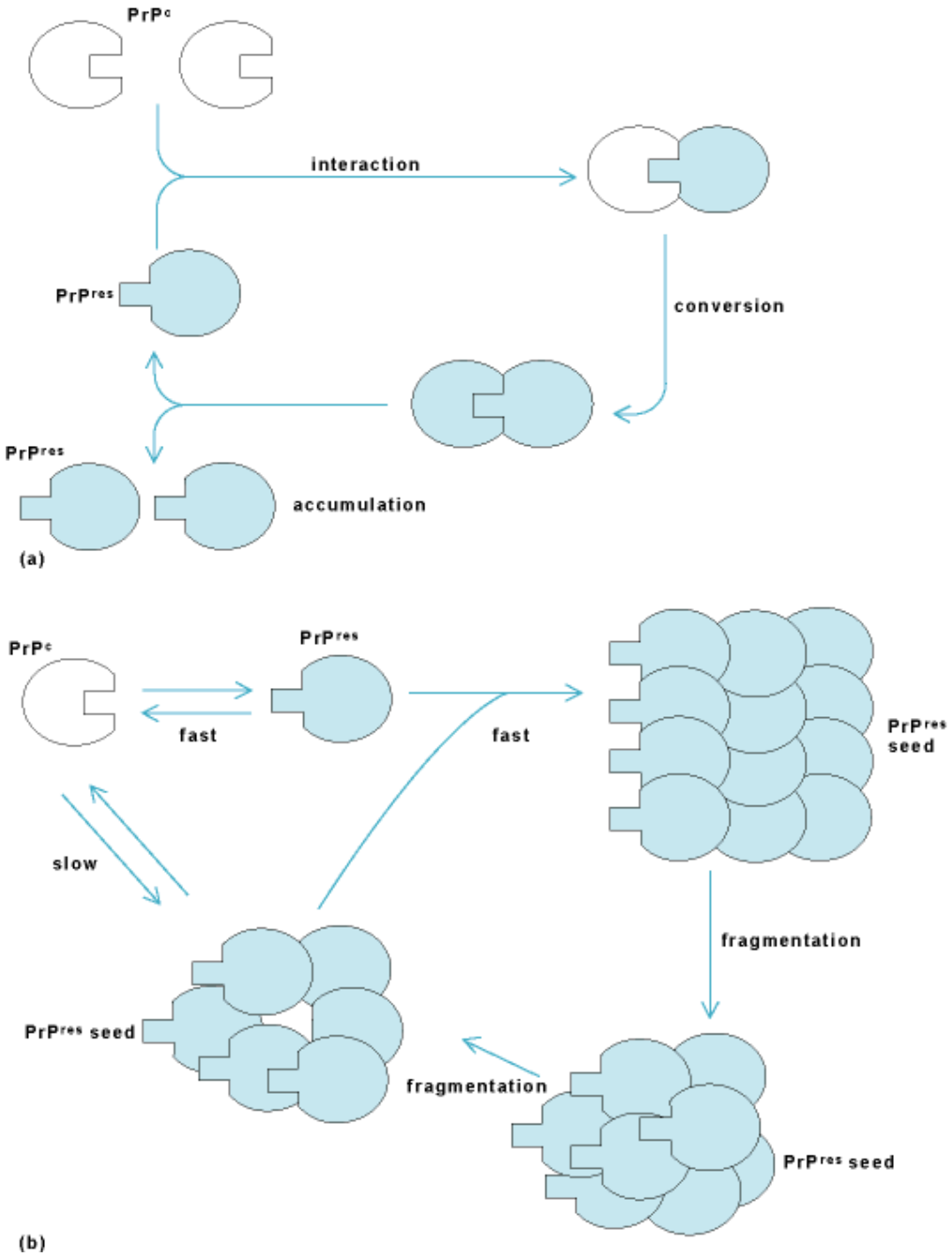

Fig. 1 Models for the conversion of normal prion protein (PrPC) into prion protein resistant to proteolytic enzymes (PrPres). (a) The heterodimer model postulates the formation of dimers between PrPC (open symbols) and PrPres (filled symbols).
Upon binding, PrPres induces refolding of PrPC into PrPres, which in turn can induce formation of additional PrPres molecules by an autocatalytic process. (b) The seeding (nucleation-dependent polymerization) model postulates that PrPres aggregate serves as a seed onto which monomeric protein deposits, adopting its conformational structure. The polymer can then be fragmented, and the new seeds generated by this process can start nucleation-dependent polymerization again.[2,4,5]

Classification

Prion diseases can be classified according to the mechanisms by which they develop (that is, the forms) and the characteristics of the disease that they cause (that is, the phenotype). Thus, the sporadic form is thought to be caused by the random misfolding of normal prion protein, resulting in the spontaneous formation of the aberrant protein. The inherited form includes diseases linked to one of a number of mutations in the prion protein gene; these mutations are likely to facilitate the spontaneous conversion of prion protein into the resistant form by destabilizing the native structure of the protein. Finally, the acquired forms occur as a result of an infectious process initiated by the introduction of abnormal prion protein-containing material from the outside.[2, 4]

Forms and Phenotypes

All inherited forms of prion disease are associated with specific mutations (changes in amino acid sequence) of prion protein.[1, 2, 4] These mutations include replacement of a single amino acid with another, deletion of part of the prion protein molecule, and addition of one or more units of an eight-residue-long amino acid sequence. An important feature of the prion protein is the polymorphism at amino acid residue number 129, which can be either

methionine or valine. This polymorphism modulates the risk of acquiring the sporadic and the transmitted forms and can modify the disease phenotype. The mutation at codon 178 causes a disease called fatal familial insomnia when associated with a methionine codon at position 129, and a familial form of Creutzfeldt-Jakob disease when associated with the 129 valine codon. The mutation at codon 200 resulting in the substitution of the amino acid glutamic acid with lysine is the most common mutation associated with familial Creutzfeldt-Jakob disease, while the 102 mutation replacing proline with leucine is commonly associated with Gerstmann-Straussler-Scheinker disease.[2, 4] Overall, prion diseases are rare, with the incidence of about one case per million persons a year. About 85% of the cases are sporadic. All inherited and sporadic forms occur in adults; the age at onset of the acquired form depends on the time of infection. The incubation time varies between 16 and 28 months when the brain tissue is directly contaminated, and 5 and 15 years when the infection occurs peripherally. [1,2, 4] The Creutzfeldt-Jakobs disease phenotype associated with the familial, sporadic, or iatrogenic forms is characterized by dementia and disturbances of gait and vision.[1] Brain tissue changes can be detected only under the microscope and are characterized by the presence of small spongelike holes, referred to as spongiform degeneration. [1, 4] Features of fatal familial insomnia include inability to sleep and severe loss of nerve cells in a region at the center of the brain called the thalamus. The Gerstmann-Straussler-Scheinker disease phenotype most often includes a slowly progressive gait disturbance and other disturbances due to cerebellar dysfunction; the microscopic pathology is distinct for the presence of amyloidlike deposits. [1, 2, 4] The capacity to spread through an infectious mechanism potentially makes prion diseases a serious threat to public health. [1, 2, 3, 4, 5]

Prion Epidemics

Over 200 cases of the infectious form of the disease have been transmitted through medical interventions; these cases are commonly referred to as iatrogenic (pertaining to a

secondary condition arising from treatment of a primary condition) Creutzfeldt-Jakob disease.[1, 4] The carriers of the infection are implants of contaminated human tissues, such as the cornea and the external layer of the brain covering called dura mater, the hormones extracted from the pituitary gland, and contaminated surgical instruments.[2] The first evidence that prion diseases can be acquired by the ingestion of contaminated food was provided in the 1950s by the discovery of kuru, a disease affecting endemically a New Guinea tribe that practiced cannibalism.[2] A prion disease of sheep and goats called scrapie has been known for over two centuries, but no cases of human transmission have been recorded.[1, 2] A major epidemic of a prion disease affecting cattle, called bovine spongiform encephalopathy or mad cow disease, broke out in the United Kingdom in 1986. Bovine spongiform encephalopathy was transmitted by meat and bone meal derived from infected cattle and other ruminants that had not undergone appropriate denaturing treatment during the rendering process. The epidemics peaked in 1992 and are now rapidly receding. To date, mad cow disease has affected approximately 200,000 cows from over 34,000 herds.[1, 2] A few years after the bovine spongiform encephalopathy epidemics, a new human prion disease with a phenotype distinct from that of sporadic Creutzfeldt-Jakob disease was observed in the United Kingdom.[2] To date, 21 cases of new ariant Creutzfeldt-Jakob disease have been reported in the United Kingdom and one in France.[2] The major features that distinguish new variant Creutzfeldt-Jakob disease from the typical type include earlier onset and the widespread presence in the brain of microscopic prion protein deposits surrounded by vacuoles, named daisy plaques.[1, 2]

Conclusion

Substantial evidence has been accumulated to indicate that new variant Creutzfeldt-Jakob disease might have been acquired from bovine spongiform encephalopathy-affected cattle. The link between animal and human forms of the disease justifies the precautionary measures that have been instituted throughout Europe and the U. S.

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