A Review Article

Prion Diseases : (I) The Etiology of Prion Diseases

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Abstract:

Prion diseases or transmissible spongiform encephalopathies (TSE's) constitute an unusual group of progressive neurodegenerative disorders of man and animals characterized clinically by dementia, neurologic and motor disturbances, and ultimate fatality, and pathologically by neuronal vacuolations, gliosis and astrocytosis in the brain tissue. These diseases are peculiar in that they are both infectious and inherited, and are the only known diseases believed to be caused by an "infectious" protein. That protein is a protease-resistant, insoluble prion protein capable of replicating in neurons in the absence of nucleic acid; it is referred to as the "prion protein of scrapie," or PrP^{SC} , and is believed to arise as a result of misfolding of its normal counterpart in the cells, PrP^{C}.

Prion diseases have come into prominence following overwhelming outbreaks of bovine spongiform encephalopathy (BSE) in the U.K., and subsequent diagnosis of the so-called variant Creutzfeldt-Jakob disease, a zoonotic version of BSE, in numerous human victims. A voluminous amount of research into prion diseases has since been published.

Although the prion model is currently the most favoured etiologic model of these diseases, several other hypotheses have been forwarded to explain the nature of the causative agent(s), including "virus," "virino," "chaperone" and "lysosomal storage disease" hypotheses. None of these hypotheses has so far been conclusively proven or ruled out. In part I of this review, the current status of knowledge on the etiology of prion diseases and the different hypotheses of possible etiologic agent(s), with special emphasis on the nature of prions, are discussed. In part II, the clinical and pathological aspects of prion diseases affecting man and animals, and the advances in their diagnosis and treatment, are described.

Introduction

Prion diseases are a group of peculiar degenerative disorders of the brain affecting man and animals. They are widely believed to be caused by a

modified, "infectious" version of an apparently ubiquitous cellular protein known as prion protein (PrP). Prion diseases are also known as “transmissible spongiform encephalopathies” (TSE) because although some of them are inherited, all of them can be transmitted experimentally by inoculation or ingestion of infected material. Once the genetic form of the disease arises, the victim's brain becomes "infectious" as well. Therefore, prion diseases are both infectious and inherited – in fact; they are the only known diseases that combine these two attributes. A less commonly used name for prion diseases is transmissible cerebral amyloidoses (TCA) [1].

Prion diseases are generally characterized by a long incubation period, usually measured in years, a relatively short clinical course, and a 100% mortality rate. Almost invariably, they cause dementia, loss of motor control, paralysis and ultimately death [2]. Microscopic examination of the brain shows different degrees of degeneration of the brain tissue, with presence of spongiform intracytoplasmic neuronal vacuolations and loss of neurons, especially in the cerebellum and cortical areas of the brain stem. These changes are accompanied by extensive microglial activity and proliferation of astrocytes - cells responsible for support and repair in nervous system - in the affected regions [3]. The activated microglial cells release inflammatory mediators, including prostaglandins and free radicals, which may enhance neuronal damage. Pocchiari [4] reported that CSF samples from patients with Creutzfeldt-Jakob disease (CJD) contained increased levels of prostaglandin E2 (PGE2) and 8-epi-PGF2, as compared to patients with non-inflammatory neurologic disorders, indicating the occurrence of inflammation and oxidative stress in CJD. This author also reported a short survival in CJD patients with high CSF levels of PGE2, suggesting that the inflammatory response is correlated with the clinical duration of the disease [4].

A common feature of all prion diseases is the presence of fibrils or plaques of an abnormal protein in and around the brain cells [5]. These fibrils were previously referred to as scrapie-associated fibrils (SAF) but following elucidation of their chemical nature, they are now called prion protein of the scrapie type (PrP^{SC}) or protease resistance prion protein (PrP^{res}). The presence of this abnormal protein distinguishes prion diseases from other brain diseases that cause dementia such as Alzheimer disease [5].

Though the nature of the infectious agent of prion diseases has not yet been definitively proven, the idea that PrP^{SC} itself is responsible both for the infectivity and pathogenesis of these diseases is widely accepted, and that is why they are now more commonly referred to as “prion diseases.”

Nature of Prion Disease Agent(s)

Prions are defined as "*small, proteinaceous infectious particles that resist inactivation by most procedures that inactivate nucleic acids"* [6]. The resistance of these proteins to nucleases, enzymes that digest nucleic acids, and irradiation, suggests that they lack a nucleic acid genome. In other words, the protein alone is the infectious agent. This protein is highly resistant to protease K, in contrast to its isoform that occurs naturally in the neurons and many other cells types and is readily digested by protease K. The harmful, K-protease resistant form of the prion protein has been named PrP^{SC} or PrP^{res} [7], while the harmless, naturally occurring counterpart is named PrP^{C}, the superscripts are used to distinguish the type of prion: “SC” refers to "scrapie" or "scrapie-like”, “res” refers to “protease-resistant” and “C” refers to "cellular" [5]. In this review, we shall use PrP^{C}, for the harmless and PrP^{SC} for the harmful isoforms of prion protein.

2. Prion Disease Theories:

Originally, prion diseases were believed to be caused by unidentified slow viruses; this was based on the infectious nature and filterability of the putative etiologic agent. However, all attempts to demonstrate virus or virus specific nucleic acid, including the use of subtraction hybridization analysis techniques, have failed to find a nucleic acid in scrapie-infected brains that is not found in normal brain [5]. On the other hand, evidence of the prion hypothesis is becoming increasingly more convincing and many biologists have now accepted that a modified prion protein (PrP^{SC}) alone is the cause of these diseases, and that modified protein could replicate without the presence of nucleic acid. Others, however, are still questioning the validity of this hypothesis, and believe that the so-called “prion” does have an independent genome that is yet to be discovered, the most important evidence in this regard being the existence of several, distinct mutable "strains" of the scrapie agent, with different incubation periods and different pathology, which implies the existence of genetic information in a nucleic acid of the infectious particles [8; 9]. Accordingly, there are now two main

hypotheses regarding the agent(s) of prion diseases: prion hypothesis and virino hypothesis (virino is a small strand of infectious nucleic acid wrapped in protein). In recent years, a third hypothesis, chaperone hypothesis, has also emerged, which considers the prion to be a molecular chaperone that becomes spontaneously misfolded [10]. There are several other less popular hypotheses on the etiology of prion diseases.

2.1. ***Prion Hypothesis*:**

Prion diseases have three peculiar features: (i) they are caused by an infectious agent that does not seem to require a nucleic acid to replicate (ii) they are both infectious and inherited and (iii) the causative agent has an unusually high resistance to heat, desiccation, freezing, stomach acid, pH changes and various other chemical and physical methods that are normally used to destroy viruses, bacteria and fungi.

The idea that the agent might be a protein capable of replication in the absence of nucleic acid dates back to the 1960's, when Tikvah Alper - a British microbiologist at Hammersmith Hospital - and her colleagues exposed the brains of scrapie-infected mice to ultraviolet radiation. She used UV doses sufficient to destroy nucleic acids, and found that the irradiation did not abrogate the infectivity of the brain tissue. Accordingly, she proposed that scrapie and other related diseases such as Kuru might be caused by an agent that did not require nucleic acid for replication [11]. At that time, her views were ridiculed because it was unconceivable that an infectious agent could replicate without either RNA or DNA. Fifteen years later, Alper's idea was revived by Prusiner [12], who described novel properties for the "scrapie agent" that distinguish it from viruses, plasmids and viroids. Prusiner showed that the scrapie agent was indeed highly resistant to all known procedures of nucleic acid inactivation, while losing its infectivity as a result of treatment with protein denaturing procedures. He proposed the new term "prion" for the scrapie-agent in order to denote its proteinaceous and infectious nature, while distinguishing it from viruses. Since then, Prusiner and his colleagues have conducted extensive research on the physical, chemical, biochemical and molecular properties of PrP, and its genetics and mode of replication. These studies suggested that the development of prion diseases involved structural modification of a harmless, naturally occurring PrP^{C} into the harmful PrP^{SC} version [2; 12-

19]. A year before Prusiner's original paper proposing that the scrapie agent was a prion protein was published [12], Merz, at the Institute for Basic Research on Developmental Disabilities, Staten Island, New York, reported that brains of scrapie infected mice contained strange fibrils [20]. The occurrence of error in protein folding was also mentioned by Griffith since 1967, when he wrote: "perhaps a protein that wouldn't normally adopt a particular folding pattern could be catalyzed to do so by a protein that had already assumed that shape" [5]. However, it was Prusiner who pursued this concept and performed extensive studies to support it, work that convinced many biologists and gained him the Nobel Prize.

According to the prion hypothesis, all TSE's or prion diseases are protein conformation disorders leading to accumulation of PrP^{SC} in the brain. The PrP protein is a sialoglycoprotein that occurs on the surface of neurons and other cells [21]. It is held to the cell surface by a glyco-phosphoinositol or GPI. Its function is not precisely known, but it is probably involved in the work of synapses as well as copper binding and cell signaling [1; 22]. PrP is encoded by a chromosomal gene that seems to be highly conserved, since it is found in diverse organisms ranging from fungi and insects to human beings. In humans, this gene is found in the short arm of chromosome 20 [23]. The normal and harmful types of prion protein are isoforms with the same amino acid sequence, but differing in conformation. The structure of PrP^{C} is composed predominantly of lengthy coils known as α-helices, with no β-pleated sheets, while the amino acids in PrP^{SC} molecules are folded into β-pleated sheets, with very low α-helix content [24-27]. In contrast to PrP^{C}, the PrP^{SC} molecules tend to form insoluble aggregates and fibrils in the brain that resist proteases, and these aggregates and fibrils are the cause of neuronal destruction. It is not known precisely how the misfolded prion damages the neurons, apart from accumulating in them, but one possibility is that it is toxic. Another possibility is that it deprives neurons from PrP^{C}, which could be essential for their survival, though this argument is countered by observations that mice did not sustain harmful consequence for up to 500 days after knocking out their PrP gene [5].

In prion disease, the conversion of PrP^{C} into PrP^{SC} is a post-transcriptional event that occurs either as a result of acquiring PrP^{SC} molecules via some form of horizontal transmission, or as a result of

mutation in the gene responsible for prion production (Fig 1). According to Prusiner [14], whenever a PrP^{SC} molecule comes in contact with a PrP^{C} molecule in the neuron, it induces the PrP^{C} molecule to change its conformation into a PrP^{SC} conformation, and the newly formed PrP^{SC} molecule, in turn, induces another PrP^{C} to change conformation, and so on. This chain reaction mechanism of refolding allows the abnormal prion to "replicate" without need for specific nucleic acids (Fig 2). It is also possible that infection with the abnormal prions speeds up nucleation-dependent polymerization of the protein molecules, leading to rapid production of PrP^{SC}. Both the refolding and polymerization models involve direct interaction between PrP^{C} and PrP^{SC}. In the refolding model, the conversion of PrP^{C} into PrP^{SC} is catalyzed by the formation of PrP^{C}-PrP^{SC} heterodimer. In the polymerization model, the rate determining step is the formation of a nucleus of polymerized PrP^{SC}, and once that nucleus is formed, it promotes further polymerization [14; 28; 29]. As these insoluble, enzyme-resistant PrP^{SC} molecules accumulate in increasing quantities in brains cells, they destroy the cells. When the cells are destroyed, the PrP^{SC} molecules are released and could enter and destroy new cells.

As stated earlier, PrP^{SC} formation can also be induced by mutations in the PrP gene. These mutations occur in the open reading frame (ORF)[1] of the gene and have been found in all families with inherited prion diseases; the mutations are believed to initiate the disease by destabilizing one or more α-helices of PrP^{C}, leading to its conversion to PrP^{SC}, which then replicates in the manner described above [25]. Studies on genetically engineered mice showed that mice into which the mutant gene was transferred developed prion disease spontaneously, whereas mice with normal PrP gene developed the disease only after injecting PrP^{SC} into their brains. On the other hand, when the PrP gene was removed, the animals could not develop prion disease if injected with PrP^{SC} into their brain. When neurons that make up PrP^{C} were grafted into these mice whose PrP gene had been knocked out, and the mice then inoculated with the scrapie agent, their susceptibility was re-established; the grafted tissue became filled with

[1] Open reading frame (ORF) of a DNA segment is a potential protein sequence identified by an initiator codon in a frame with a chain terminating codon. Special computer programs are used to search for these sequences.

degenerative neurons while the rest of the brain remained unaffected [7; 30]. These experiments suggested that whether a host will develop prion disease or not depends *both* on exposure to the abnormal prion, and the presence of the PrP gene.

Additional support for the prion hypothesis comes not only from the fact that PrP^{SC} fibrils are invariably found in all prion diseases, but also from observations that the quantity of PrP^{SC} is proportional to the severity of the condition, and that the more the PrP^{SC} preparation is purified, the more infective it is [20]. Furthermore, while the infectivity of PrP^{SC} is not affected by different types of disinfection that destroy microbes nor by nucleases that digest nucleic acids, the infectivity can be reduced by substances that cause protein denaturation such as strong alkalis. Furthermore, when PrP^{SC} is denatured and then renatured, it regains infectivity [2]. Additionally, prion disease patients do not show features commonly found in viral infections such as fever, significant inflammatory changes, inclusion bodies or immune response. On the other hand, in all cases of hereditary prion diseases like GSS or FFI and inherited CJD, the patients have the mutant gene that produces PrP^{SC}. In total, these inherited forms make up 25% of all prion cases [15].

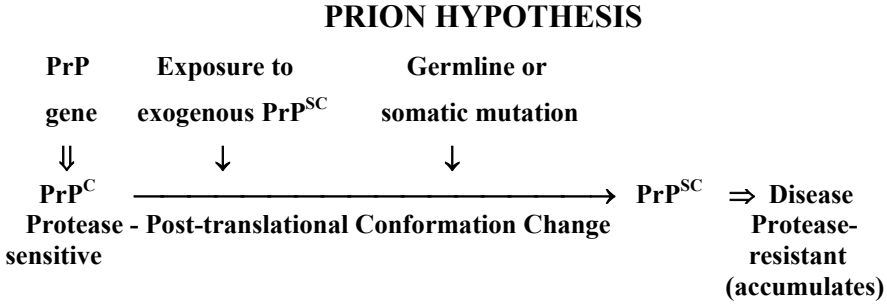

Fig 1: Prion Hypothesis: Prion diseases are caused by accumulation of abnormal isoform of prion protein in neurons. This abnormal, protease resistant protein or PrP^{SC} is formed as a result of post-transcriptional change in the conformation of a normal, protease-sensitive cellular prion PrP^{C}. Either exposure to PrPSC from an outside source or germline or somatic mutation in the PrP gene induces this conformational change. Adapted from Jackson [31].

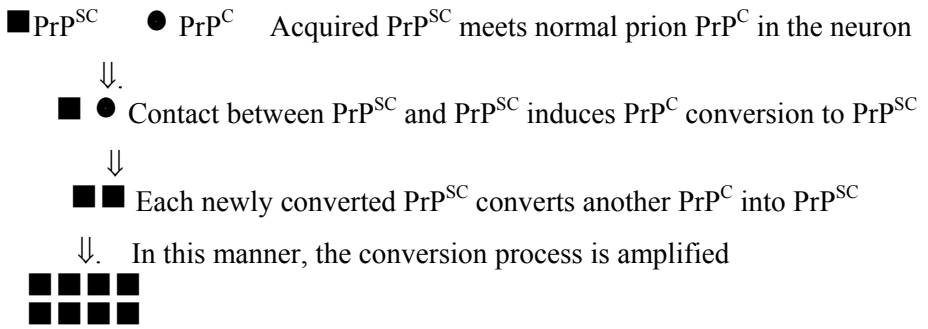

Fig 2: Prion Hypothesis: If harmful prion PrP^{SC} comes in contact with normal cellular prion PrP^{C} in the neurons, it induces PrP^{C} to change its conformation to PrP^{SC} conformation. The newly transformed PrP^{SC} in turn induces another PrP^{C} molecules to change conformation. A chain reaction occurs leading to accumulation of large amounts of PrP^{SC} in the neurons, and destroying them and causing disease. Adapted from: Annon. [20].

2.2. *Virus/Virino Hypotheses*:

Although the prion hypothesis has been accepted by most biologists, it is not universally accepted, since it represents a major deviation from the biological dogma that nucleic acids are essential for protein synthesis and replication of infectious agents [20]. Many biologists therefore believe that the search should continue for an unconventional virus, or rather a virino[2], as the cause of prion disease should continue.

Supporters of the viral hypothesis argue that PrP might be an important element in disease development - e.g., it could be a host-cell receptor that directs an unknown virus into the cell and thereby control susceptibility - but there must be a nucleic acid that controls its synthesis. They also argue that abnormal prion (PrP^{SC}) could be an intermediary or a product of cell destruction, rather than the cause of it [20; 32].

[2] The virino hypothesis replaced the virus hypothesis following studies suggesting that the average size of nucleic acid per "infectious unit" is not more than 80 nucleotides (Kellings et al., 1992).

Some of the features of prion diseases are commensurate with viral infections. For example, although prion diseases have many features in common, there are differences between them such as differences in the length of the incubation period and host range, as well as changes in the infectivity of different organs and tissues during different stages of disease. Another important consideration is the existence of a species barrier for infection, which could be attributed to a reduced affinity of a given viral agent to PrP^{C} of a different host species. But probably the strongest argument in favor of a viral agent is the existence of different, mutable "strains." Bruce and Dickinson [8] reported several distinct “strains” of the scrapie agent, each with its own characteristic properties, with respect not only to the incubation period length, but also to the pattern and distribution of brain pathology. The properties of these strains remain unchanged by repeated passage in the same mouse strain, with homozygous PrP gene, indicating the existence of genetic information specific for each strain. These findings, coupled with occurrence of considerable mutations, suggested that the agent of scrapie has an independent, replicating genome, and that it could be a small virino (nucleic acid molecule coated by host protein) that awaits discovery. If true, that “virino” must be highly unconventional not only in terms of its size, which is apparently smaller than the size of any known virus or viroids [33], but also in terms of its resistance to treatment with nucleases and other nucleic acid modifying agents. Those in favor of the virino hypothesis argue that the size of the nucleic acid doesn’t have to be large, since it doesn’t have to code for any protein, while its unusual resistance to nuclease-modifying agents - such as nucleases, hydroxylamine and psoralins – can be due to the protective effect of its host-derived coat.

Westaway *et al*. [19], on the other hand, argued that since PrP is encoded by the human genome, variations in the gene sequence could have a profound effect on the occurrence and course of disease, and the length of the incubation period. Prusiner et al. [25] also argued that differences between "strains" do not necessarily mean presence of genetic information specific for each strain, but rather that the prion protein adopted different conformations, with consequently different effects. Furthermore, they stated that the infectivity of a certain type of PrP^{SC} depends on how closely it resembles the host's own prion.

Hecker *et al*. [34] introduced the so-called "targeting hypothesis" in which they suggested that strain-specificity is determined by the cell subtypes in which the propagation of PrP^{SC} molecules took place. By contrast, Bessen *et al*. [35] and Kocisko et al. [36] reported that species-specific PrP conversion into protease-resistant forms could be achieved in a cell-free system, although the possibility cannot be ruled out that some cell-type specific components that conferred strain-specificity might have "contaminated" the cell-free culture via PrP preparations.

On the other hand, numerous transmission studies suggested that when infective material is transmitted from one species of animal to another, as for example when mice are inoculated with scrapie infective material from sheep, the required dose is initially extremely high, the incubation period is prolonged and the pathology of the disease is altered. However, after repeated passages of the infection in the new species, in this case the mouse, there is a dramatic reduction of the incubation period, which becomes stabilized at a new value. Besides, when a species becomes infected with a prion disease of a different species, it can transmit the infection more easily to other members of its own species, and may also infect a wider range of new species that the original host could not. All of this has to do with the existence of a *species barrier*, which offers a strong argument in support of a viral etiology. To verify that question, an important experiment was conducted by Scott *et al*. [37] in which they showed that if a hamster PrP gene was inserted into mice, this would remove the species barrier between the two species; i.e. when a mouse into which the hamster PrP gene was inserted is injected with scrapie from a hamster, the mouse would develop scrapie as if it were a hamster [Fig 3]. This was taken as evidence that the PrP protein, rather than a virus, was the "infective agent" and since this protein is produced from the genes of the host animal, it has a different structure in different species, and that is why the host barrier exists [15; 16].

Nevertheless, it must be emphasized that the capability of prion protein to replicate in the absence of nucleic acid could only be proven unequivocally if the misfolded prion (PrP^{SC}) is synthesized in a way that totally eliminates any possible presence of nucleic acid, then injecting this synthetic prion and observing whether it replicates or not. So far, all attempts to achieve that have been unsuccessful [20].

Finally, in an attempt to reconcile the concept of infectious protein, which explains the existence of "strains" on the basis of stable variations in the PrP^{SC} molecules, with the virino concept, which explains "strains" on the basis of nucleic-acid encoded information, Weissmann [28] introduced the so-called "unified theory," in which he suggested that PrP might be associated with a host-derived episomal nucleic acid, which encoded for strain-specificity but was not essential for infectivity.

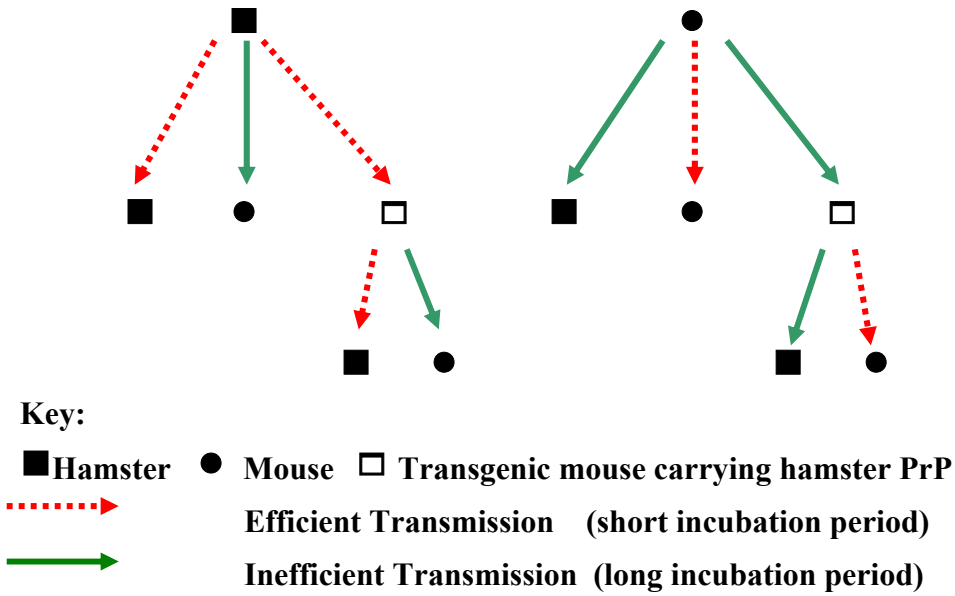

Fig 3: Species Barrier: If prions are transmitted from a mouse or hamster to another animal of the same species, the disease develops in the recipient after a comparatively shorter incubation period, but if prions are transmitted from one species to another, e.g., from mouse to hamster, the disease develops after a much longer incubation period, or not at all. However, if the "hamster" prions were passaged repeatedly in the mouse, the incubation period of the disease in the mouse decreases dramatically and stabilizes at a new value. This is called "species barrier" and was considered to be an evidence of viral infection. However, it was found that if you introduce the PrP of the donor species (the hamster) into the recipient species (mouse), the latter animal becomes as equally susceptible to the hamster prions as the hamster. From Heaphy [6].

2.3. *Chaperone Hypothesis*:

This hypothesis does not violate the dogma that replication occurs only in the presence of nucleic acid. It has been found by spectroscopic methods that conversion of PrP^{C} to PrP^{SC} involves profound conformational changes, which probably require a chaperone mediator [38- 40]. Chaperones are proteins that direct the folding and unfolding of other proteins, and the chaperone hypothesis is based on the suggestion that a certain protein factor(s), called X factor, which might be a chaperone, is involved in the formation of PrP^{SC} [15]. It has been suggested that PrP^{SC} itself could be protein X or the chaperone that produces the conformational change. However, studies on the interactions between PrP^{C} and PrP^{SC} do not support this argument [15; 23]. Some heat shock proteins are also known to act as chaperones, and it has been found that some changes do occur in the inducibility and the distribution of these proteins in scrapie-infected cells [10; 38-40].

With the identification of an increasing number of "conformational" diseases, or protein misfolding diseases, the chaperones are becoming the focus of increasing interest and considerable research is currently underway to design novel chaperone drugs to correct the structural problem.

Other Hypotheses:

The massive outbreak of bovine spongiform encephalopathy (BSE) has triggered numerous other hypotheses about the possible causative agents of prion disease. One of these hypotheses suggests that prion diseases could be lysosomal storage diseases and there are studies suggesting that the site of PrP transformation is the lysosome itself [41]. Other hypotheses have incriminated autoimmune reactions, bacterial toxicosis, chemical agents, glycosidase inhibitors and a host of other factors in the etiology of prion diseases, but none of these has in fact been adequately substantiated.

Conclusion:

Although several hypotheses have been put forth to explain the propagation of the prion disease agent(s), two hypotheses, namely the "prion only" and the virino hypothesis, have been the focus of greatest attention. While neither of them has been unequivocally confirmed or ruled out experimentally, the hypothesis that PrP protein might be the sole component of the infectious prion disease agent has gained a much wider popularity because of consistent failure to identify a specific "foreign" nucleic acid in prion diseases despite extensive search.

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استعراض علمي
أمراض البريون : (١) العوامل المسببة لأمراض البريون

منصور بن فارس حسين و سعود بن إبراهيم المفرج
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الملخص :

تشكل أمراض البريون أو الاعتلالات الدماغية الإسفنجية المعدية مجموعة فريدة من الأمراض العصبية التنكسية في الإنسان والحيوان، وتتميز هذه الأمراض إكلينيكيا بالخلل العقلي (العته) و الاضطرابات العصبية والحركية، فالموت، ومن الناحية الباثولوجية بالتنكس الفجوي للخلايا العصبية، والدباغ و ارتشاح الخلايا النجمية في نسيج المخ.

وبخلاف جميع الأمراض الأخرى فإن أمراض البريون هي الوحيدة التي تعد أمراضا معدية و وراثية في آن معا، كما أنها الوحيدة التي يسببها على ما يبدو نوع من "البروتين المعدي" يسمى بريون وهو بروتين محور يقاوم الأنزيمات الحالة للبروتينات ويمكن "التكاثر" داخل الخلايا العصبية في غياب أية حموض نووية. ويشار إلى ذلك البروتين الممرض بالبريون المقاوم للهضم (PrP^{res}) أو بريون مرض الرجفان (PrP^{SC}) ويعتقد انه يتكون نتيجة للتحور في تشكل نظير غير ممرض للبروتين نفسه، موجود بشكل طبيعي في خلايا الجسم ويشار إلية باسم البريون الخلوي (PrP^{C}).

وقد ازداد الاهتمام بدرجة كبيرة بأمراض البريون وذلك في أعقاب حدوث الوباء الهائل لجنون البقر (اعتلال الدماغ الإسفنجي البقري) في بريطانيا، وما تلاه من اكتشاف عشرات الحالات من مرض كروزفلد جاكوب المغاير الجديد في الإنسان، والذي ينجم عن اكتشاف العدوى من البقر إلى الإنسان. وقد نشر عدد كبير من البحوث حول هذه الأمراض في الآونة الأخيرة.

ورغم أن نموذج البريون المحور كمسبب لأمراض البريون هو الأكثر قبولا في الوقت الراهن، فإن هناك فرضيات أخرى عدة حول طبيعة العامل المسبب لهذه الأمراض ومنها فرضية الفيروس والفيرينو و"الرقيب" (Chaperone) وكذلك فرضية أنها من الأمراض التخزينية للأجسام الحالة، ولكن لم يتم حتى الآن إثبات أي من هذه الفرضيات أو استبعادها بشكل قاطع.

هذا ويتناول الجزء الأول من هذه الاستعراض العلمي ما تمت معرفته حتى الآن عن مسببات أمراض البريون والفرضيات الأساسية حول طبيعة تلك المسببات وآليات تكاثرها.أما الجزء الثاني فيتناول السمات الإكلينيكية والباثولوجية لأمراض البريون في الإنسان والحيوان وما تمت معرفته حتى الآن عن تشخيص هذه الأمراض وإمكانية علاجها.