



Review

Approaches to therapy against prion diseases focused on the individual defence system

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Abstract: Prion diseases are neurodegenerative disorders for which no effective treatment is available to date. Misfolded protein as aetiological agent is currently the most accepted theory. This review is focused on the hypothesis that the main basis of the progress of these disorders might fall on the individual defence system. Host protective response could convert into the early cellular event that triggers further brain tissue destruction. Specifically, neuroglial cells as main immunological cells located in brain might be influence on the pathogenic process of neurodegeneration by interaction with neurons. As consequence, neuroglia would be established as a turning point in therapeutic strategy of prion diseases. This alternative seems particularly desirable due to that they would result more effective than curative treatments trying to act on the irreversible neurodegenerating process. Moreover, all advances attained in the frame of this therapeutical approach result especially relevant for other neurodegenerative diseases such as Alzheimer's, Parkinson's or Huntington's diseases, Frontotemporal dementia or Amyotrophic Lateral Sclerosis which are currently considered prion-like disorders since aberrant proteins spread throughout the brain during disease progression in all of them, and thus they may share molecular basis and mechanisms of propagation.

Keywords: neuroglia; prion and prion-like diseases; therapy; astrocytes; microglia; neurodegeneration; neuroinflammation; autoimmunity

1. Introduction

Prion diseases consist of a group of transmissible neurodegenerative disorders which affect animal as well as human species (Scrapie, Bovine Spongiform Encephalopathy (BSE) or chronic wasting disease; and Creutzfeldt Jakob disease (CJD), Gerstmann-Straussler-Schienenker (GSS), Fatal Familial Insomnia or kuru, respectively). To date it has been impossible to develop preventive and/or palliative treatments against these pathologies; then, they possess an unavoidably lethal final. A protease-resistant form, conformationally altered, of the prion protein (PrP_c) termed PrP^{Sc} is considered critical for this group of diseases. In fact, the prion protein as aetiological agent causing this group of diseases is the most accepted theory since it was postulated by Prusiner SB in 1982. PrP_c exists in healthy animal cells while they are attached to cell membrane [1]. It is considered that this protein is cytotoxic in its unbound state, when it is accumulated in cytosol [2]. Since the brain is less efficient than other animal organs in its ability to remove abnormal molecules, PrP^{Sc} can be found accumulated in this kind of diseases.

2. Immunological involvement

While most authors claim this protein as infectious itself [3-8] some others postulate it as consequent feature [9-11]. The possibility of this protein as triggering of a host response which might cause the neurodegeneration may constitute an alternative hypothesis, not only for prion but also for other neurodegenerative disorders. Despite prion theory is the most widely spread some authors have proposed that the misfolded protein is probably the result of evolution of a self-defence reaction. Axelrad [9] suggests that any T-cells that recognize anchor PrP, in the absence of initiating chemicals, would enter a state of immunotolerance to the protein; only when immune response is either experimentally or accidentally triggered by unbound PrP, devastation of tissue begins. Differences in treatment of PrP by the host protective system could explain those cases where prion disease-like symptoms can be transmitted to mice in the absence of detectable abnormal prion protein [10] or why up to 25% of cows with suspected BSE possess no spongiform symptoms at autopsy, probably due to resistant genotypes [9].

An autoimmune response may even represent a supported theoretical hypothesis for these diseases [11], because it makes possible to explain some of these difficult unsolved questions. The interactions between astrocytes and oligodendrocytes observed by Liberski et al. [12] in CJD and Scrapie infected mice may support this possible autoimmune response, due to that the association of these cells does not seem to be associated with a reaction towards any infectious pathogen. Rather, they may also represent an early cellular event that triggers further brain tissue destruction. This could be mediated by pro-inflammatory cytokines secreted by astrocytes, lymphocytes and macrophages. It had been already suggested that TNF α secreted by astrocytes may be responsible for some brain tissue destruction encountered in prion diseases [13]. And it is important to point out that both TNF α and its mRNA are massively up-regulated toward terminal stage of experimental CJD in mice [14,15]. But moreover, not only astrocytes are the only source of cytokines in prion diseases, but also microglial cells [16]. Microglia, the main phagocytic cell in central nervous tissue which are associated with the pathogenesis of many neurodegenerative and brain inflammatory diseases [17], have been demonstrated to serve as sensitive indicator of local neuronal damage predicting degeneration of neurons [18]. It is known to be present in Scrapie affected mouse brains and even to

be a component of amyloid plaques in kuru, CJD and GSS [19,20]. However, although all these data lend support to the hypothesis that this glial population is clearly involved in the pathogenesis of CJD, its expression/alteration has been studied in only some murine Scrapie models [21] and few CJD cases [22,23]. In addition, it results interesting to mention that pro-inflammatory cytokines have been implicated in pathogenesis of multiple sclerosis, a neurodegenerative disorder whose source is accepted to be autoimmune. Otherwise, very insufficient efforts have been made to deepen on this possible immunological involvement regarding neurodegenerative diseases.

Furthermore, several groups have shown evidences of humoral immune responses in prion diseases. Gadusek's group found that sera from Scrapie affected sheep were reactive mainly to neurofilament protein preparations from mouse brain [24]. Increased levels of antibodies to bovine myelin basic protein, neurofilament and prion antigens were also detected in BSE animals [25,26], as well as of IgG, IgA and C3 in the cerebrospinal fluid and IgA in serum belonging to CJD patients [17]. And CJD and kuru patients have shown elevated values of myelin basic protein auto-antibodies [28] and anti-neurofilament antibodies [29]. Additionally, the inoculation with prion disease affected brains has failed to produce clinical disease when cells B were absent [30]. Accumulation and activation of microglial cells have been observed in prion affected animals and CJD patients [31], and elevated plasma levels of C reactive proteins and IL6 cytokines, both indicative of ongoing inflammation somewhere, have been detected in CJD [32]. Besides, Hu et al. [33] revealed PrPc as a molecule critically influencing T cell functions, by modulating TCR signals and limiting survival.

An amazing aspect of prion diseases is the fact that they are accepted to be associated to some different types or strains [34-36]. Strain typing based on the differences among PrPsc glycoforms and this glycosylation proportions have been determined. Nevertheless, just those establishing differences among human CJD types [37] and BSE and natural Scrapie affected sheep [38] have been extended and routinely applied afterwards because inconsistent results are provided in many occasions. Moreover, even regarding human subtypes which are quite well established, variability is also observed depending on the methodology applied. In fact, two similar but not identical classifications, Parchi and Gambetti's and Collinge's, are currently accepted. Since, according to the "only protein" theory, prion consists of an agent lacking in nucleic acid, prion strains differentiation is based on their phenotypical features determination. Additionally, it is accepted that for the identification and characterization of a strain it is strictly necessary a bioassay using murine models; however, it depends on the murine line, and some other additional factors, some strains inoculated can behave in disagreeing manners and present different molecular and/or phenotypical profiles. All these observations appear to be supporting the responsibility of host processing to determine the molecular profile in each human or animal case.

With regards to transmissibility, despite all enormous attempts mainly made focused on *in vivo* diagnostic purposes in order to provide repetitive and conclusive results, infectivity has been demonstrated in samples such as blood [39,40], where no PrPsc has been detected to date. Other disagreeing results have been, and continue being provided depending on the model and the protocol designed. While some authors have described infectivity of a tissue or biological fluid in all cases, some others conclude that no risk at all is shown in it [41]. But moreover, it is advisable not to forget that these studies about transmissibility in these pathologies have been based on the inoculation of nervous central system homogenates (and not purified prion protein). Therefore, some other antigens capable to initiate the individual's immune response could be also present in these homogenates.

3. Neuroglia in neuroinflammation

On the other hand, although not many efforts have been made to go into this topic in greater depth, an interaction of agent and host influencing in the development of the disease has been suggested [42]. In fact, gliosis constitutes one of the histopathological changes typically found in the brains of human and animal cases joint to neuronal degeneration and deposit of pathological prion protein, but scarce relevance has been certainly pinpointed to the components of this cellular population in the pathogenesis of prion diseases until the recent hypothesis about neuroinflammation regarding neurodegenerative diseases. With the aim of demonstrating which role these glial cells are playing in the pathogenesis of the prion disease, first studies have been developed on the natural model of Scrapie, demonstrating the indisputable involvement of astroglia in prion progression by showing specific changes of this glial population matching up to the evolution of the disease [43] and which can sustain active prion propagation [44]. Moreover, experimental studies using primary cellular cultures have recently demonstrated that glial cells respond to prion infection through Toll-like receptor mediated innate immunity [45]. These findings as a whole suggest that drawing interactions between microglia and astrocytes may hold an important key to understand neuroinflammation in prion and other neurodegenerative disorders. It might also open up new immunotherapeutic strategies.

Therefore, it seems to be concluded that all these observations strongly suggest that components of neuroglia in charge of brain protection could perform a crucial role in the pathogenesis of prion diseases. It could be even therefore speculated that the differences in the development and progression of the disease expressed by different neurodegenerative courses, may lie in differences in the MHC class II epitope presentation in the central nervous tissue [46]. So, the expression of different phenotypical profiles above referred as subtypes or strains could be associated to the different progress of the individual's protective reaction against the antigen. In fact, to determine whether a specific MHC class II epitope is expressed in a higher percentage of CJD and Scrapie cases would constitute an interesting contribution to support the immune hypothesis, due to that it is well known that this frequently happens in immunity disorders. In fact, a very recently published study has even suggested that misfolded proteins rescued from protein degradation by MHC class II molecules are recognized as "neo-self" antigens by immune system and constitute autoantibody targets [47].

Further deciding evidence that supports an actual role for host defence system in the onset of prion diseases are those showing in Magri et al. [48]. Their results not only showed an increased amount of pro-inflammatory cytokines in infected compared to uninfected animals, but also suggest that immunization achieved in mice using synthetic oligopeptides homologous to hamster prion protein significantly reduces inflammation. Therefore, the protective effect of the vaccination seems to be due to the consequent inflammation reduction. The proposal elaborated by De Luigi et al. [49] indicating that tetracyclines might have therapeutic potential for animals and humans against prion diseases, confers another contribution for supporting the relevance of the inflammation in the development of prion diseases. The authors suggest that these antibiotics reduce prion infectivity through a direct interaction with PrP^{sc} potentially inactivating BSE and variant CJD (v-CJD) contaminated products [50]. However, it exists the possibility of that their evidenced efficiency is caused due to the anti-inflammatory effect presented by this family of antibiotics [51] more than the direct interaction of antibiotic with PrP^{sc}. In fact, it has been proved to have effect on diseases where

no infectious agent is involved [52]. Additionally, several studies have been published concerning the neuroprotector and neuroinflammatory effect of some tetracyclines in neurological diseases. The neuroprotector effect seems to be based on the inhibition of apoptosis by caspase-dependent mechanism [53]; meanwhile, the anti-inflammatory effect is thought to be due to the microglia modulation, by decreasing the consequent inflammatory mediator expression [54].

4. Neuroinflammation in prion and prion-like diseases

As it is recently accepted that inflammation represents a common denominator among a diverse list of neurodegenerative diseases, it seems to be implicated as a critical mechanism responsible for the progressive nature of neurodegeneration. Neuroinflammation itself is considered either causative or at least, contributory to the pathogenesis of neurodegeneration [55]. Since there are few therapies for the wide range of neurodegenerative diseases, scientists are still in search of new therapeutic approaches to the problem. Prostaglandins and cytokines, such as interleukin-1 (IL-1) and interleukin-6 (IL-6), have been implicated in the aetiopathology of various inflammatory and degenerative disorders, including Alzheimer's disease (AD) and prion diseases [56]; therefore, an early contribution of neuroprotective and anti-inflammatory strategies for these disorders seems particularly desirable, maybe more effective than other treatments against neurodegeneration (irreversible process, as it is known).

Concerning the possible stimulus which could trigger an exacerbated immune response, some researchers have named as possible candidate the Phosmet, an organophosphate pesticide [57]. But this theory is difficult to sustain since Scrapie has been known some hundreds of years before the discovery of organophosphates by the chemical industry [11]. In fact, an experimental study to elucidate the role of some organophosphates in the source of prion diseases, finally provided results which discarded this hypothesis [58].

For some authors, microbe agents such as *Acinetobacter* or *Pseudomonas* could be the antigen causing this initial response. These bacteria might have evoked prion diseases through the mechanism of molecular mimicry and autoimmunity in similar way to *Streptococcus* microbes producing rheumatic fever and Sydenham's chorea. The proposed pathogenic mechanism is that susceptible patients when exposed to repetitive or high load of the bacteria would produce increased levels of antibodies to the bacterial antigenic molecules as well as auto-antibodies to the cross-reacting brain antigens. The end result of these immunological reactions is inflammation, degeneration, axonal damage and vacuolation in the affected areas [59]. In fact, it is known that *Acinetobacter* is a microbe containing molecular sequences which resemble those found in neurofilaments of the brain tissue and therefore, some authors suggest that both can be sharing some epitope [60] causing the cross-reaction. A possible mechanism of how TSEs could be produced is illustrated by the human arthritic disorder ankylosing spondylitis, an autoimmune disease where high titres of auto-antibodies are evoked by the presence of *Klebsiella* in bowel flora. In the same manner, the inclusion of intestinal contents in green offal material in the framework of the undisputed introduction of meat and bone meal preparation in the foodstuff of cattle in early 1980s is very likely to be a source of the many microorganisms found in the soil reservoir, especially *Acinetobacter* and their antigens [61]. Repeated infections with these bacteria would evoke an immune response to the cross-reactive neuronal auto-antigens with the resultant pathological lesions. They would be mainly due to the effects of antibody-triggered, complement-mediate cytolytic or cytotoxic immune activity.

Tissue distributions and the characteristics of the lesions may vary considerably; spite of the causes are not exactly known, it could be due to influence of other environmental and genetic factors [11]. Even more, similarities and differences demonstrated between pathological lesions in experimental autoimmune encephalomyelitis, multiple sclerosis and prion diseases could be explained by different auto-antibodies against a group of heterogeneous self-antigens homologous with antigens present in some bacterial agents (such as *Acinetobacter* or *Pseudomonas*). All these links may unveil the possibility that induction of prion diseases in animals inoculated with brain tissue could be due to an exacerbated immune response to injected brain antigens [11]. It is essential to keep in mind that central nervous tissue is known to express the largest variety of proteins in the body [62].

Some other relevant contributions which have mainly served to emerge the proposal about the relevance of host are for instance, the fact that it has been widely assumed that consumption of meat from BSE-affected animals may have caused death in about 200 v-CJD cases diagnosed to date (National CJD Surveillance Unit). However, nutritional studies carried out by this Surveillance Unit have failed to show higher meat consumptions in v-CJD patients compared to controls. Even the description of v-CJD in patients who had been vegetarians for a number of years was epidemiologically evaluated. These findings should have raised doubts, but the theory based on the consumption of meat- bone meal as the vehicle of transmission of v-CJD to humans and BSE epidemics (the bovine infectious variant of prion diseases), remains the most accepted theory.

Finally, it is important to remark that studies have been increasingly published showing more and more neurodegenerative diseases affecting, progressing and behaving in a similar way than prion diseases. Alzheimer's, Parkinson's and Huntington's diseases, frontotemporal dementia or amyotrophic lateral sclerosis are currently thought to be caused by prions [63] and are called prion-like diseases, indeed.

Specifically, Alzheimer's disease as the most worldwide common prion-like disorder occupies a similar spectrum of symptomatic pathologies with prion-mediated encephalopathies. They are both dementing disorders involving deposition of extracellular protein aggregates with associated neurodegeneration, characterized by a cascade of events that end with extracellular deposition of amyloid- β (A β) or PrP^{Sc} fibrillar peptides, respectively. CJD risk, as with Alzheimer's disease, is usually increased by the APOE4 allele [64,65]. Meanwhile, APOE2 allele lowers the risk of both of them. Moreover, there is an association between homozygosity at *PRNP* codon 129 (Met versus Val) and early onset Alzheimer's disease [66,67]. According to biochemical and histological studies, APOE possesses binding affinity for A β and PrP and is associated with A β plaques of Alzheimer's disease brain and kuru-like plaques [68,69]. Furthermore, it co-purifies with the protease-resistant core of PrP (PrP²⁷⁻³⁰) extracted from brains of hamsters with experimental Scrapie [70]. And a final relevant coincidence is that oligomeric A β possesses infectious prion-like features under certain situations, inducing cerebral β -amyloidosis and associated pathology in transgenic mice by intra-cerebral administration of exogenous A β -containing brain extracts from human with Alzheimer's disease [71,72]. Additionally, patients where both pathologies were found have been also reported [73]. All these findings, further those showing that both PrP^{Sc} and A β preferentially bind PrP^{Sc} as oligomers, raise suspicion of a common downstream mechanism, even suggesting these two neurodegenerative stimuli competing for pathway modulation [74].

Concerning the role of neuroglial cells in Alzheimer's disease, it is being dealt with not long ago [75-77]. And results support the hypothesis presented here. Specifically, some authors point out the novel NG2 as glial cells playing an important role in this neurodegenerative disease pathogenesis [78]

based on their highly proliferative ability and capacity to regeneration of neurons and astrocytes in adult cortex [79]. But moreover, similar findings have been consistently found in patients suffering CJD and Alzheimer's disease when the involvement of astroglia was comparatively assessed in both neurodegenerative processes [80]. Additionally, a relationship between both microglia and astroglia has been just suggested to induce neuron death in various neurodegenerative disorders such as Alzheimer's, Parkinson's or Huntington's diseases, amyotrophic lateral sclerosis and multiple sclerosis [81].

5. Conclusion

By this evidenced analogy of prion-like with prion diseases, all advances attained in the frame of therapeutical approach result especially relevant, not only for prion disease study, but also for other prion-like diseases. More supporters are nowadays gaining the hypothesis which postulates that they all share molecular basis and mechanisms of propagation. Consequently, in case the involvement of host defence system is indisputably confirmed in prion pathogenesis, the design of new therapeutic alternatives for all these neurodegenerative diseases is feasible.

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Conflict of interest

The author declares no conflict of interest.

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