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The architecture of prions: how understanding would provide new therapeutic insights

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Summary

Compelling evidence from the last three decades clearly shows that transmissible spongiform encephalopathies (TSEs) develop as a result of a poorly understood misfolding event that converts the cellular prion protein (PrP^{C}) to an isoform known as PrP^{Sc} which is aggregated, protease resistant and able to impose its aberrant conformation onto PrP^{C}, leading to its accumulation in the central nervous system. Despite all the knowledge gathered in more than thirty years of research and the general understanding of the pathological processes, the molecular mechanisms remain elusive, making it difficult to develop rational therapeutic strategies for this group of incurable diseases. In this review article, we give an overview of what is known about prion architecture and how the limited structural information available has been used in the quest for remedies for these devastating disorders.

Key words: *prion diseases; transmissible spongiform encephalopathies (TSEs); misfolding proteins; therapeutical approaches*

Introduction

Since Stanley Prusiner proposed the "protein only" hypothesis three decades ago [1], research in the field of transmissible spongiform encephalopathies (TSEs), a group of fatal neurodegenerative disorders affecting several mammalian species including humans, has been focused mainly on the misfolded prion protein PrP^{Sc}, widely accepted as the causal agent. Human prion diseases (which include Creutzfeldt-Jakob disease, Gerstmann-Sträussler-Scheinker disease and familial fatal insomnia among others [2]) and animal prion diseases (such as scrapie in sheep and goats [3], chronic wasting disease in cervids [4], bovine spongiform encephalopathy in cattle [5] or transmissible mink encephalopathy [6]) all share some common features including spongiform degeneration of the central nervous system (CNS), amyloid plaque formation, neuronal loss and reactive gliosis [7]. All those pathological hallmarks were linked through the "protein only" hypothesis to the presence in the CNS of a 27 to 30 KDa protease-resistant protein named PrP27-30 or PrP^{Sc} (scrapie-associated prion protein), a derivative of the single gene encoded, protease sensitive, 30–35 KDa cell-surface glycoprotein known as PrP^{C} (cellular prion protein) [8, 9].

Compelling evidence from the last three decades clearly shows that TSEs develop as a result of a poorly understood misfolding event that converts the PrP^{C} to PrP^{Sc}, which is found aggregated, is protease resistant and able to induce its aberrant conformation in PrP^{C}, leading to its accumulation in the CNS [1]. Depending on the source of PrP^{Sc}, prion disorders can be classified as infectious if the PrP^{Sc} is acquired from external sources, genetic if the PrP^{Sc} is produced internally due to disease associated mutations in the PrP encoding gene, or sporadic if the PrP^{Sc} is formed as a result of spontaneous misfolding of the wild type PrP^{C} [10–12]. TSEs can manifest as phenotypically distinct diseases in animals that share identical PrP sequences, known to be caused by different PrP^{Sc} conformers, named strains [13–15]. How these distinct pathogenic isoforms emerge has been difficult to understand and fit within both Prusiner's theory and the mechanistic rules governing the variable ability of interspecies transmission of the different prion strains [16, 17].

Despite all the knowledge gathered in more than three decades of research and the general understanding of the pathological processes, the molecular mechanisms remain elusive, making it difficult to develop rational therapeutic strategies for this group of incurable diseases. Specifically, the central process of TSEs, the conversion of PrP^{C} to PrP^{Sc}, together with the strain diversity and interspecies transmission, are all structurally determined [18, 19], so to definitively solve the three-dimensional structure of all the proteins involved would be a great step forward towards the design of new rational strategies that could interfere with prion propagation and disease progression. However, it must be stressed that several compounds interfering with the pathological process have been found by phenotypic screening on *in vitro* and *in vivo* model systems, regardless of structural features. This is the case for compounds such as pentosan polysulphate [20, 21] or other sulphated glycans [22, 23] that prevented PrP^{Sc} accumulation in cell culture and prolonged survival times in mice models [24]. Similarly, some amyloid-binding sulphonated dyes, such

as Congo red [25], suramin [26] or curcumin [27], have long been known to inhibit PrP^{Sc} accumulation. Cyclic tetrapyrroles, compounds with a highly conjugated planar ring system that bind transition metal ions, were also reported to inhibit PrP^{Sc} accumulation *in vitro* and prolong survival times upon early administration *in vivo* [28, 29]. A possible mechanism of action has been recently described at a single-molecule level using force spectroscopy [30]. Other anti-prion compounds worth mentioning include tetracyclic compounds [31, 32] and lysosomotropic compounds such as quinacrine, chlorpromazine and quinine [33–35]. However the use of many of the molecules listed is hampered by severe adverse effects or poor blood-brain barrier permeability, among other disadvantages, leading to the design of derivative compounds that may solve these problems and enhance their antiprion activity.

Although all these, and several other compounds, were discovered in the absence of structural knowledge about PrP isoforms, a better understanding at the molecular level of the interactions between the compounds and PrP^{C} or PrP^{Sc} would be highly valuable for a more rational optimisation or derivative design. Other strategies will be only briefly described, as this review is mainly focused on therapeutic approaches that could derive from new structural insights on the central event of TSEs, the misfolding of PrP. Some of the most interesting approaches for the treatment of TSEs that do not involve direct interaction with PrP and thus could be developed regardless of structural features include: (i) perturbation of lipid rafts for PrP^{C} sequestration or redistribution [36–40]; (ii) suppression of PrP^{C} expression through siRNAs [41, 42]; (iii) targeting accessory molecules or pathways to conversion [43–47]; (iv) enhancing PrP^{Sc} clearance [48–50]; and (v) use of neuroprotective agents as symptomatic treatment [51–53].

However, in this review article we intend to offer an overview of what is known about prion architecture and how the limited structural information available has been used in the quest for remedies for these devastating disorders.

The known part of prion architecture, PrP^{C}

The PrP^{C} is the only element involved in the central process of PrP^{C} to PrP^{Sc} conversion that has been structurally characterised at a high resolution level (fig. 1). Although several models have been proposed during recent years, neither PrP^{C}/PrP^{Sc} interactions nor the PrP^{Sc} fibril structure have been solved yet, and the lack of knowledge is clearly proven by the strikingly different molecular models suggested (table 1).

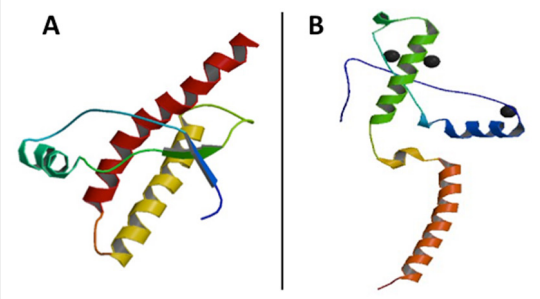

Figure 1

Three dimensional structure of PrP^{C} solved by (**A**) nuclear magnetic resonance (PDB code 1QM1) and (**B**) X-ray diffraction (PDB code 1I4M).

The cellular form of PrP is a cell membrane protein, generally found in lipid rafts, which is comprised of an unstructured N-terminal and a globular C-terminal domain. The latter consists of three α-helices, and a β-sheet formed by two antiparallel β-strands that during its maturation undergo a few posttranslational modifications such as glycosylphosphatidylinositol (GPI anchor) attachment, addition of up to two N-linked glycans and the formation of a disulphide bond that connects the C-terminal α-helices [54–59]. Despite the detailed structural information available, the physiological role of the C-terminal domain remains uncertain and many different functions have been proposed, such as copper regulation [60, 61], signal transduction [62, 63], immune system modulation [64–66], programmed cell death inhibition [67, 68] and so on. Nonetheless, some of the previously suspected functions of PrP are being reassigned to other proteins. Some robust studies seem to confirm its role in neuroprotection and myelin maintenance [69], finally starting to separate the wheat from the chaff in the large number of functions attributed to PrP^{C}.

Even though it is widely accepted that PrP misfolding is the central event in disease pathogenesis [70], the exact mechanism by which the misfolding occurs or even the exact composition of the protein form causing the prion disease has not yet been identified [71]. Hereditary or familial forms of the disease clearly establish that some single point mutations, mostly located in the globular domain of the PrP, as well as insertions or deletions found in other regions, increase the tendency to misfold [72–78]. Similarly, several monoclonal antibodies known to bind to specific motifs of the globular domain are able to prevent prion disease in animals [79–82]. Knowledge of PrP^{C} structure, as well as studies that indicate that different regions of the protein are critical for the initial misfolding steps [83–87], have led to the rational design of strategies for PrP^{C} stabilisation. Although initial attempts to stabilise PrP^{C} were made with well-known molecular chaperones [88] or compounds previously found to bind PrP^{C} regardless its structure [28, 89–93], descriptive and structural studies on PrP mutants [94] and the binding sites for PrP^{C}-stabilising compounds are proving useful for the detection of key regions and design of new therapeutic strategies. This is the case with some recent studies, where PrPs with distinct pathological point mutations [95] or protective polymorphisms [96, 97] were analysed in depth to reveal their structural basis, in order to counteract or mimic their effect. This is in line with the search for point mutations or polymorphic variants that increase the thermodynamic stability of PrP^{C} [98]. Most of the research done on PrP^{C}-stabilising compounds is still based on chemical modification of drugs previously found effective in model systems or structure-activity studies with large chemical derivative libraries [34, 99–103]. It should be noted that the latter studies can be performed without any knowledge of the structural arrangement of PrP^{C}. However, very promising approaches

based on knowledge of PrP^C structure and *in silico* modelling [104], such as the NAGARA tool developed by Ma and collaborators, are leading the way to the new era of rational drug design [105].

The unknown part of prion architecture, PrP^C/PrP^{Sc} interaction and PrP^{Sc} structure

One of the big unsolved questions concerning PrP^C to PrP^{Sc} conversion is the molecular mechanism by which PrP^{Sc} induces its aberrant conformation in PrP^C. Models mimicking this phenomenon *in vitro* have clearly shown the selective binding of both isoforms of PrP [106], and further studies on PrP^C/PrP^{Sc} binding and interspecies transmission revealed some putative interaction sites [106–110]. However, the prion strain diversity and the many different putative binding sites found suggest that interaction between isoforms is mechanistically complex and highly precise. There are two main theoretical models describing this phenomenon: heterodimer polymerisation [111], in which conformational conversion to PrP^{Sc} is templated by contact with monomeric PrP^{Sc}, and autocatalytic seeded polymerisation [112], in which conversion is induced by polymeric PrP^{Sc}. Blocking this PrP^C/PrP^{Sc} interaction with molecules that bind either to PrP^C or PrP^{Sc} is an important therapeutic target where the lack of structural details impedes the design of rational strategies. Thus, proper identification of interacting sites and detailed mechanistic description of this process are of vital importance. Some molecules have been found to interfere in this process, among which dominant negative inhibition strategies stand out. These approaches are based on the addition of heterologous PrP^C or PrP fragments known to be poorly convertible through interspecies transmissibility studies or through the finding of protective PrP variants [107, 113, 114]. Moreover, other rational approaches are based on computational searches of chemical compounds that mimic the spatial orientation and polymorphisms of the key PrP residues that confer dominant negative inhibition [115].

Apart from therapeutic actions against PrP^C/PrP^{Sc} interaction, actions on the neurotoxic PrP species and PrP^{Sc} disaggregation or degradation need to be considered. Again, the detailed molecular mechanisms behind prion-induced neurotoxicity, PrP^{Sc} structure and aggregate clearance are still unsolved, impeding the rational design of treatments focused on reduction of toxicity, blockade of PrP^{Sc} fibril growth or enhanced aggregate degradation. Concerning neurotoxicity, compelling evidence indicates that fibrillar PrP^{Sc} deposition is not directly linked to neurodegeneration and to the existence of oligomeric species associated with toxicity [71, 116, 117]. However, the great variety of misfolded oligomeric forms detected hinders identification of the really toxic and infectious ones, impeding any therapeutic action against them. Furthermore, how these unknown neurotoxic forms of PrP exert their effect on the nerve cells is another open question, although several mechanisms have been proposed, such as induction of apoptosis by activation of the complement pathway [118], by formation of pores in the cell membranes [119, 120], by specific modulation of N-methyl-D-aspartate (NMDA) receptors [121] or by inhibition of the proteasome [122]. The importance of accurately assessing the cytotoxic mechanism was highlighted by the toxicity induced by some antiprion monoclonal antibodies through binding to certain epitopes on the PrP^C [123, 124]. This suggests a possible role for PrP^C in the neurotoxic pathway and that, until this pathway is properly characterised, any therapeutic strategy based on molecules binding to PrP^C is potentially toxic. Protein homeostasis is also known to be altered in disorders caused by protein misfolding, and some evidence indicates that its impairment might be an early mediator of prion-induced neurodegeneration through repression of global protein expression or activation of pro-apoptotic pathways. In this case, therapeutic efforts are targeted on components involved in those pathways, regardless of the structural features of the PrP species inducing neurodegeneration [124–128].

Finally, the last unsolved mystery related to PrP^C/PrP^{Sc} conversion that could contribute to the development of rational therapies is the three-dimensional structure of the PrP^{Sc} aggregates. Despite being a research topic of tremendous importance in order to reach a complete understanding of the prion diseases and one of the first entities associated with the pathology, its difficult purification, insolubility and aggregated state have limited the reliable structural data obtained. Hopefully, infectious recombinant prion generation in *in vitro* systems may soon help to overcome some of these issues related to sample amount and purity, allowing the acquisition of high-resolution structural data [129]. The variety of biophysical techniques applied to the resolution PrP^{Sc} aggregate structure has yielded equally variable data and thus led to the publication of several different molecular models (table 1) [130–139]. Such differing models as the parallel in-register extended β-sheet model with no α-helix proposed by Cobb [130] and the β-solenoid modelled by Wille [131] illustrate the controversy surrounding the real structure of infectious prions. Moreover, none of the molecular models proposed fits entirely with all the experimental structural data available [140], although they could be partially correct or even describe different possible arrangements for misfolded PrP, highlighting the tremendous importance of an accurate identification of infectious versus noninfectious PrP polymers that are definitely generated *in vitro* [141] and may also be present *in vivo*. Given the lack of reliable structural information, it is not yet possible to design rational therapeutic candidates at the PrP^{Sc} level, although some interesting strategies have been proposed that take advantage of the limited structural information available. This is the case for rational vaccine design based on disease-associated epitopes through identification of PrP regions exclusively exposed in its misfolded conformation [142], which illustrates the advantage of even partial structural information. But with a few exceptions, compounds promoting fibril stabilisation or clearance have been mainly found through screening for amyloid-binding compounds or structure-based design of their derivatives, with poorly understood mechanisms of action [143–146]. Compounds that are known to be effective against other protein misfolding-related disorders that share some pathological features with prion diseases [147–151] have also become an important

source of anti-amyloidogenic compounds [152–154]. However, many of the compounds tested had blood-brain barrier permeability issues, toxicity or strain specificity problems that hindered their clinical application. The strain specificity of some apparently successful compounds, clearly shown by Berry and collaborators [155], is alarming as it suggests that a general treatment for prion disorders might be impossible unless structural differences between strains are described in detail. Moreover, prions have been shown to acquire drug resistance under selection pressure of antiprion compounds, probably through slightly different structural variants already present as subvariants of the strains or "quasi species" [156–158]. This poses a problem not just for therapy development but also for the structural study of prions that seem to appear as a heterogeneous structural mix. Although other interesting therapeutic approaches have been explored and are being developed that do not require PrP^{Sc} structural knowledge, such as engineering disaggregases [159, 160], and inducing expression of kinases [161, 162] and heparanases [21, 163], direct actions against PrP^{Sc} imply the need for reliable structural models of the infectious and neurotoxic agent.

Altogether, this overview of the current knowledge on mechanistic data about prion pathogenesis and the possibilities opened for rational therapy design states clearly the urgent need of accurate molecular models that would enable a significant step forward in the treatment of these still incurable diseases.

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Table 1: Main features of different structural models proposed for the three dimensional structure of PrPSc. (Adapted from reference [73]).

Model	Description	Acceptance	Reference
Four-stranded β-sheet with two α-helices	Based on a truncated version of PrPSc (108–218) constructed by combining computational techniques and experimental data from the secondary structures of PrPSc from CD and FTIR studies. It suggests a four-stranded β-sheet that conserves two C-terminal α-helices.	Recent experimental observations do not support the interpretation of FTIR measurements on which this model was based.	[132]
Antiparallel intertwined β-helix	Molecular modelling of possible β-helical structures is based on primary sequence arrangement, assignment of conformations based on established examples of β-helical conformations and potential tertiary anti-parallel conformations. This results in strands of antiparallel β-sheets projected from an antiparallel intertwined core that expands into eight β-strands.	The height of eight β-strands predicted by this model is in contradiction with the X-fibre diffraction results [131].	[133]
Parallel β-helix	Characterisation with electron crystallography of two infectious variants of the prion protein, two dimensional crystals of truncated PrPSc (27–30) and a miniprion (PrPSc106) that indicate the existence of a parallel β-helix in the core. Given the low resolution of the technique, they could be left-handed or right-handed parallel β-helices.	Recent experimental observations do not support the presence of C-terminal α-helices that this model predicted.	[134]
Five-stranded β-sheet with C-terminal α-helices	Model based on sequence analysis and X-ray diffraction data on recombinant PrP that suggests a dimerisation mechanism. It was modelled from the human TATA-box binding protein structure, which is a five-stranded β-sheet that in the case of PrP conserves the C-terminal α-helices.	Recent experimental observations do not support the presence of the C-terminal α-helices.	[135]
Spiral model	Molecular dynamics simulation was used to model the structural change of a recombinant PrP at acidic pH. This resulted in a spiral model where the original α-helices from PrPC are conserved and up to four β-strands are also formed. A fibrillary structure was proposed where the β-strands angles are not perpendicular to the fibril axis.	X-ray fibre diffraction data [131] is incompatible with β-strand angles not perpendicular to the fibril axis. Moreover the high α-helical content does not fit with FTIR and limited proteolysis data.	[136]
Left-handed β-helix "Govaerts"	Based on the previous parallel β-helix model and higher resolution electron micrographs of the same two-dimensional crystals of truncated PrPSc (27–30) and miniprion (PrPSc106). It shows a crystal composed of trimeric cells and results in a left-handed β-helical model with the C-terminal conserving the α-helix.	Recent experimental observations do not support the presence of the C-terminal α-helices.	[137]
Left-handed β-helix "Stork"	Molecular dynamics was applied to study the stability of small polyglutamine β-helices in solution. Based on these findings, a β-helical model was proposed. The model contains a sequence alignment different from the model proposed by Govaerts et al, but similar in many other features.	Recent experimental observations do not support the presence of the C-terminal α-helices.	[138]
Two rung β-helix	Based on previous left-handed β-helix models and using molecular dynamics, the β-helical structural model was refined and a more stable arrangement proposed. Unlike the previous models, instead of four β-helical rungs per PrP monomer, a fibril composed by two rung monomers was suggested. This model is denser, with a tighter packing of helices and half of the height per monomer.	The height per monomer proposed does not match with that observed in X-ray diffraction studies [131] and the presence of α-helices at the C-terminal is also no longer supported by recent experimental data.	[139]
Parallel in-register β-sheet structure	Site-directed spin-labelling and electron paramagnetic resonance spectroscopy were used to study a recombinant PrP amyloid, showing a parallel, in-register β-sheet structure, where each monomer accounts for 4.8 Å of the fibril height.	It does not fit with the X-ray diffraction data, which indicates repeating units in the fibril that are 19.2 Å high [131].	[130]

CD = circular dichroism; FTIR = Fourier transform infrared spectroscopy; PrP = prion protein; PrPSc = scrapie-associated prion protein

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Figures (large format)

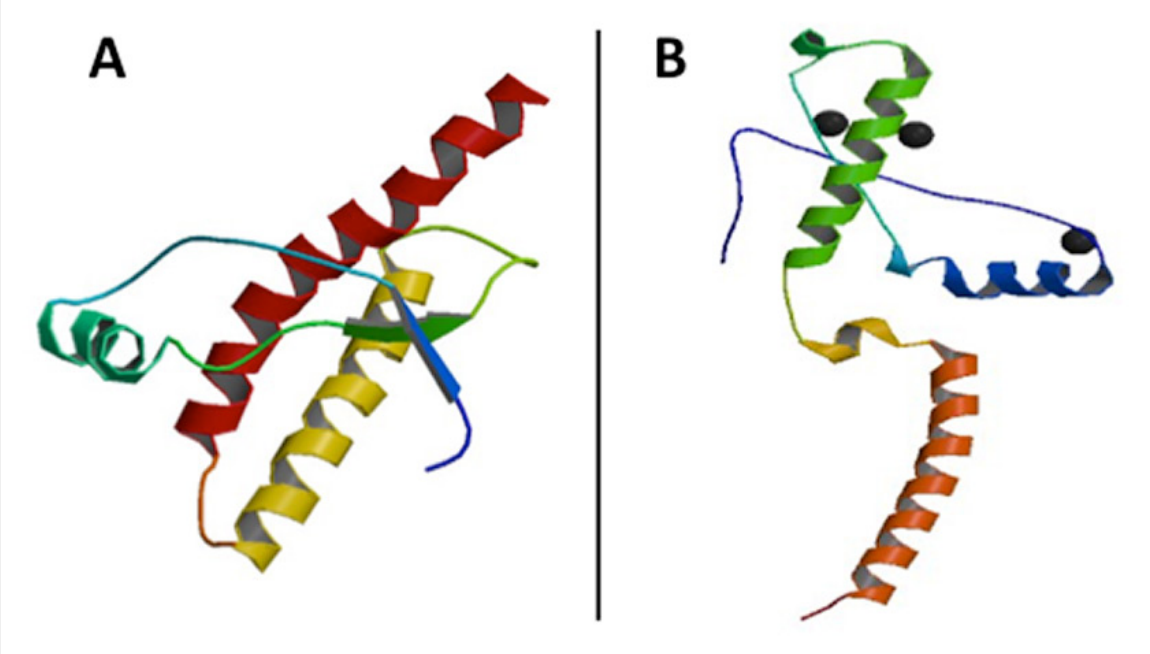

Figure 1

Three dimensional structure of PrP^{C} solved by (**A**) nuclear magnetic resonance (PDB code 1QM1) and (**B**) X-ray diffraction (PDB code 1I4M).