Synthetic Infectious Prion Formation De Novo

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Prion diseases are a class of neurodegenerative diseases that are uniquely infectious. Whilst their general replication mechanism is well understood, the components required for the formation and propagation of highly infectious prions are poorly characterized. The protein-only hypothesis posits that the prion protein (PrP) is the only component of the prion; however, additional co-factors are required for its assembly into infectious prions. These can be provided by brain homogenate, but synthetic lipids and non-coding RNA have also been used in vitro.

prions synthetic prions PMCA

1. Defining a Prion

Prions are made up of alternatively folded conformers of the prion protein PrP, which form a cross-β amyloid as opposed to the α-helices found in the native PrP^C conformer. As discussed in the introduction, two prion strain structures recently solved have a parallel in register intermolecular β-sheet (PIRIBS) structure [1][2]. While the two strains show some subtle differences, they have the PIRIBS structure in common, so it is likely that having a PIRIBS structure is a requirement for a prion. Prions typically have some level of Proteinase K (PK) resistance, and are highly stable under various denaturing conditions [3]. Prions are defined by their biological activity: they must cause transmissible disease in animals. There are however many facets to the term ‘transmissible disease’, including infectivity and toxicity, which must be carefully considered. After all, to be able to determine if a synthetic prion has been made, one must first know what a prion is or, at the very least, what a prion is not. The three traits of infectivity, toxicity and PK resistance are a good place to start when discussing what is and is not a prion.

1.1. PK Resistance

Native state PrP^C shows no PK resistance. Conversely, PK-treated preparations of infected brain homogenate contain high titres of infectivity, and PK-resistant, highly infectious assemblies of PrP (‘prion rods’) can be purified from these homogenates [4]. The core of the protein left after PK digestion of prions has been shown to vary slightly in molecular weight between different TSEs and disease strains [5], which were recently shown to correspond to distinct fibril structures [2][6]. Strains will be further discussed later. However, inoculation of suitable experimental hosts with PK-digested and undigested scrapie brain homogenates have shown that a portion of infectivity is sensitive to PK digestion and reported to be in fractions as small as a PrP dimer [7]. Another challenge to this trait is that misfolded PrP conformers have been produced, which display PK-resistance, but are not classed as prions by any other measure [8]. This means that while some prions display PK resistance, not all PrP conformers that display PK resistance are prions.

1.2. Toxicity

As prions are infectious, it follows logically that they are also responsible for the toxicity seen in prion disease, and the neurological disfunction that eventually results in death. It has however been demonstrated experimentally that toxicity and infectivity can be separated; preparations of PK-digested prion rods that were shown to be highly infectious did not display any intrinsic toxicity in primary neurons [9]. To date, no synthetic PrP conformer has been produced that is definitely toxic in animals, although several claims to this have been made, which will be discussed later in Section 4. This means that not all prions are toxic, but that the ability to cause harm is essential for a prion to ultimately cause neurodegenerative disease. It could thus be argued that self-replicating misfolded PrP conformers that deposit in the brain but do not cause neurodegeneration lack an essential component of prion disease. It is important to make a distinction between prions being directly toxic and having a toxic effect, as current hypothesis suggest that it is not prions themselves that are toxic, instead another species is responsible for the toxicity of disease [9]. This species could be a by-product of prion formation, an off-pathway amyloid PrP structure, or a non-protein component whose formation is catalysed by prions [10].

1.3. Infectivity

The trait of infectivity is what sets TSEs apart from other neurodegenerative diseases that involve protein misfolding. This infectivity is not just observed experimentally, as can be demonstrated for other diseases such as Alzheimer's [11][12][13], but is observed in the context of naturally occurring disease, such as in scrapie and chronic wasting disease. Infectivity is generally defined on the organismal level as the ability of a pathogen to invade and self-replicate inside a susceptible host. However, cell-based models, such as in the scrapie cell assay [14][15], are widely accepted proxies for measuring prion infectivity. It should be noted, though, that several amyloid species can replicate in cell models and be transmitted from cell to cell, despite not being infectious in the sense of the above definition [16][17]. True infectivity also requires continuity in the disease phenotype between the infected living systems—such as is observed in different prion strains. The protein-only hypothesis requires that all of the information required to establish a new and continuous infection in a new host must be contained within the protein [18]. Recent structural studies strongly support the view that it is encoded in the conformation of the PrP polypeptide chain in fibrillar prion assemblies [1][2]. True infectivity has not yet been reliably demonstrated for synthetic PrP conformers at titres comparable to authentic prions. However, inheritance of traits across sequential seeding rounds has been observed in synthetic systems [19], in what could be termed as in vitro infectivity.

2. Synthetic Prion Generation

2.1. PMCA

PMCA (protein misfolding by cyclic amplification) was developed as a method to allow authentic prion replication in an in vitro system [20]. Similarly to the RT-QuIC, it starts with a prion sample, the 'seed', (purified or from tissue homogenate), but typically uses PrP^C from brain homogenate as substrate for amplification. Unlike the other assays discussed here, it does not provide real-time readout (as the presence of brain homogenate would interfere

with the ThT fluorescence), instead the progression of the reaction is measured at the end point by Proteinase K resistant band intensity on a western blot. This method has been used successfully to amplify prions, which are infectious in vivo [20]. Serial rounds of PMCA amplification and dilution yield prions which statistically contain no PrP molecules of the initial seed and still retain the prion seed's characteristics [21][22]. There is debate as to whether this is truly synthetic prion generation, if the starting material is a prion. PMCA may instead provide the necessary components and conditions for genuine prion replication, without being able to form prions de novo. The use of brain homogenate also means that there are many unknown components present in unknown quantities; this means it is not a bottom-up, but rather a top-down approach to prion replication, in which components required to form a prion need to be identified from a complex mixture. Some variations on the original PMCA approach address this shortcoming by using recombinant PrP instead of crude brain homogenate, which allows for components of brain homogenate to be added individually [23]. Alternatively, recombinant PrP can be used with PrP-null brain homogenate [24].

2.2. Amyloid Seeding Assay/RT-QuIC

In vitro assays for amyloid fibril formation initially attempted to recreate the de novo formation of prion fibrils [25][26][27][28]. The seeding capacity of amyloid fibrils has been exploited for the detection of prion infection in host animals and humans [29][30]. Amyloid seeding assays (ASA), including RT-QuIC, which are based on the self-replicating nature of prions [31][32][33][34] involve adding an initial amyloid seed to an excess of native monomer under conditions that are favourable to protein misfolding, such as elevated temperatures or kinetic perturbation. Amyloid fibril growth, by the addition of monomers to the initial seed, is tracked in real-time by using amyloidophilic dyes such as thioflavin T (ThT), which show an increased fluorescence when bound to fibrils. The method was adapted to detect low volumes of prions in a sample, and these seeded aggregation assays were further developed into the RT-QuIC assay (real-time quaking induced conversion) [34][35], which is widely used for diagnostics today. These assays amplify small amounts of starting prions into a detectable readout through the use of fluorescent tags or amylophilic dyes [36]. RT-QuiC excels at sensitivity and can produce amyloid from minute amounts of seed down to a single seed particle [36]. However, since RT-QuIC assays were developed as diagnostic tools, and while they may help to distinguish prion strains [37] they do not aim to faithfully replicate prion structure, but rather to amplify PrP amyloid from a range of starting prion samples [38]. Most of the work in developing the RT-QuIC aims to improve the sensitivity of the assay and reproducibility of results [39]. Future structural studies will determine to which degree conformers formed in the RT-QuIC are identical or distinct from authentic prions.

2.3. Semi-Denaturing Amyloid Seeding Assays

The semi-denaturing seeding assay uses similar physical conditions as the RT-QuIC to accelerate fibril growth, i.e., shaking of recombinant PrP substrate with prion seed in a buffer with zirconium beads. It does not involve the elevated temperatures of RT-QuIC, but instead uses chaotropes in the buffer to partially denature the PrP^C substrate. The method uses the full length PrP or a fragment of the full protein sequence [40]. This method, or variations on it, has been widely used in the literature to produce a range of PrP conformers [29]. Some of these conformers have been described to be infectious in animal models [27], albeit with very low specific infectivity. The

assay provides a real-time fluorescence readout to track fibril growth, so the kinetics of different conditions can be analysed and compared. There is some debate as to how the initial denaturation of the monomer and the denaturing conditions affect the final structure and so properties of the fibril, and the assembly mechanism. One theory is that in the physiological disease process prions are formed in the low pH environment of the lysosome, which is mimicked by the presence of chaotropes and may partially denature PrP [41], but this is debated [42].

2.4. Native Aggregation Assays

The limitations of the above assay with regard to the denaturing conditions, and the concerns that the method does not well represent the physiological disease process, led to the development of PrP aggregation assays under near-native conditions [43]. In essence the only difference between this and the above method is the absence of any denaturant, so the protein monomer is kept in its native state. Early approaches required the presence of detergents at low concentrations [25]. Native aggregation assays in the absence of detergents require careful optimisation of reaction conditions to prevent protein precipitation whilst maintaining growth rates to fit feasible experimental time frames.

3. Non-Protein Requirements

3.1. Post-Translational Modifications

As previously stated, the substrate for a PMCA reaction originally was crude brain homogenate, but now can also consist of purified endogenous PrP^C or recombinant PrP^C. PrP^C can be purified from crude brain homogenate by detergent solubilization, Protein A agarose, PrP immunoaffinity, and cation exchange chromatography [23]. The PrP^C from this method is co-purified with equimolar quantities of 20-carbon fatty acids, which are not bound covalently to the protein. Saponification of crude brain homogenate has been shown to eliminate prion propagation [44], so it follows that lipids play a crucial role in prion propagation. Bacterially derived recombinant PrP (rPrP), while having the same amino acid sequence as endogenous PrP, does not contain any post-translational modifications. Namely, there is no asparagine N-linked glycosylation and no GPI anchor on rPrP molecules [45]. Whilst prion strains isolated ex vivo each display characteristic ratios of un- mono- and di-glycosylated PrP, the recent structural data do not yet offer a compelling explanation for these glycosylation patterns [1][2][6]. There have been reports of infectious prion generation from rPrP [46], implying that these post translational modifications are not required for prion formation. However, the efficiency of this conversion is very low, such that some labs report no infectious prion generation from the same substrate [47].

3.2. Lipids and RNA

In vitro prion replication is more efficiently supported by brain homogenate than by purified or recombinant PrP^C, suggesting some role for co-factors in the propagation of prions, perhaps as an additional component or to stabilise certain conformations [48]. It has been shown that RNA and lipids alone can support the propagation of synthetic prions [49], which naturally raised questions as to whether the nucleic acid played a role in encoding genetic

information. Using synthetic polyriboadenylic acid in PMCA reactions has confirmed that no genetic informational RNA is required to support the propagation of prions in vitro [50][51], which excludes the possibility that TSEs are caused by a virus. The co-factor activity is likely due to structural properties of the RNA interacting with the PrP. The latest high-resolution cryo-EM structures of RML prions have discovered a positively charged patch on the exposed surface of the prion [1] to which negatively charged RNA or other polyanions could bind. This binding could play a structural role in stabilising the resultant structure.

More recently, it has been demonstrated that there is a nuclease-resistant co-factor activity present in brain homogenate. Using purification and reconstitution experiments it was shown that this molecule is phosphatidyl-ethylanolamine (PE), which can act as a sole co-factor whether supplied endogenously or synthetically derived [44]. The synthetic phospholipid POPG (1-palmitoyl-2-oleoyl-sn-glycero-3-phospho-(1′-rac-glycerol)) has also been shown to support prion replication in reconstitution experiments, but only in combination with the poly-anion RNA [49].

Co-factors have been shown to play a role not only in effective propagation, but also in maintaining strain differences. By performing PMCA reactions with different combinations of RNA and POPG or with PE as the single co-factor, it was found that the same strains would form from the same co-factors. Additionally, different seeds propagated with the same co-factor would converge into the same strain. This goes some way to explaining how a single polypeptide sequence can exist stably in many different conformations; the presence or absence of different co-factors serve to influence the tertiary structure of the protein [52].

4. Current State of the Field

It has also been shown that reactions under the same conditions with the same components can cause different incubation periods in animals [53]. This suggests that different seeding competent species, i.e., different strains, were produced. Subtle difference in sonication power output could possibly cause these differences, or they could be a result of the inherently stochastic nature of the aggregation process favouring the replication of the structure that was established first [54]. It has been observed that less efficient sonication horns facilitate prion formation in purified substrates better than crude brain homogenate, while newer high-energy horns facilitate formation better with crude brain homogenate [55]. Recent structural studies on other amyloidogenic proteins have discovered a large number of structural polymorphs [56], which has reinforced the hypothesis that prions may exist as a quasispecies [57], i.e., a population of co-existing conformers generated by imperfect replication of the structural information of the prion [58][59]. It is plausible that, analogous to evolutionary fitness on the genetic level, different conformers could be selected for in replication under subtly different conditions.

Other work has reported the formation of recombinant prions from truncated (91–231) recombinant PrP, which cause disease only in transgenic mice overexpressing truncated PrP [60]. The use of truncated substrate also suggests that the synthetic prions produced may not be formed in the same way as during the disease process, so the findings may not be transferable to the wild-type disease. A large variety of different animal lines and genetic backgrounds are used to score infectivity and serial passage; some of these lines overexpress PrP, or express a

transgenic version, so do not well represent true disease. Some lines also form prions spontaneously, as noted in a number of papers where the control animals display protease-resistant PrP [52]. Recent advances in analysing prion and amyloid structures by cryo electron microscopy promise to shed light on the structures of PrP fibrils generated by different protocols and their overlap with the structures of prion rods isolated ex vivo. Whilst there is no certainty that any co-factors required for prion propagation may be incorporated into a final prion assembly, it is intriguing to note there were poorly defined electron densities in the structures of both the 263K and RML prions recently determined [1][2].

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