Prions and Amyloids—An overview

Amyloids are proteins aggregated in a cross-β-sheet conformation. While all proteins can form amyloid under non-physiologic conditions [1], only proteins with specific domains can misfold into amyloids *in vivo*. Such amyloids are "self-seeding" as they efficiently attract soluble molecules of the same protein to join the aggregate.

The aggregation of normally soluble proteins into amyloid deposits is often associated with devastating neurological disease. Amyloid-β, α-synuclein and superoxide dismutase amyloids are respectively associated with Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis (ALS) [2]. Also, prion diseases that cause transmissible spongiform encephalopathies (e.g. mad cow disease, scrapie, and Creutzfeldt Jakob disease) are all associated with amyloid deposits of the same protein, PrP.

Although all amyloids are self-seeding, not all are infectious. Unlike Alzheimer's, Parkinson's and ALS that are not known to be transmitted between organisms, prion diseases are clearly infectious. The difference may be that infectious amyloids fragment more efficiently than non-infectious amyloids, which facilitates the transmission of the small fragments called seeds.

The prion hypothesis is that infectious protein alone, without a virus, bacteria, fungus or even any nucleic acid, causes prion disease [3]. This idea was at first greeted with a great deal of skepticism. A significant advance came when infectious proteins were shown to also exist in yeast, where they cause heritable traits [4]. Indeed insertion of pure fungal prion amyloid into prion-less cells expressing the normal protein, has now been shown to infect cells with the heritable prion [5-7]. This was the long sought after proof that protein can be infectious.

The finding that inbred animals can be infected with "strains" of prion diseases that differ (e.g. in incubation time) challenged the prion hypothesis [8]. This is because it was difficult to imagine that infectious PrP could exist in multiple prion conformations. In contrast, different disease strains were easy to explain in terms of mutations in an infectious virus. Later, yeast prions were also found to exist as different "strains" where they were termed "variants" [9]. Strains and variants have now indeed been shown to be associated with distinct amyloid conformations of the same protein [10-12]. Furthermore seeds aggregated in a particular variant conformation faithfully transmit that variant conformation to the molecules they seed.

This issue of *Seminars in Developmental Biology* begins with an examination of how prion seeds work. Reviews 1 and 2 (Nelson and Ross; Bruce and Chernoff) deal with the paradox that although very small sequence changes in a prion protein can dramatically reduce seeding efficiency, nonetheless, prion seeds can enhance *de novo* prion formation of unrelated prion proteins. This and other data [13] led to the suggestion that short, rather than large, sequences drive amyloid formation. It also appears that small sequence changes can prevent molecules from joining seeds in certain variant shapes [14].

Review 3 (Crow and Li) looks at newly identified prions and discusses their potential functions. Review 4 (Saupe) describes the first prion known to be advantageous for the cell, [Het-s] of *Podospora anserina*. This prion prevents somatic fusions with cells carrying the allelic non-prion protein HET-S by killing cells that fuse. This heterokaryon incompatibility is believed to inhibit the spread of parasites. The structure of the [Het-s] prion domain is a β–solenoid. β-sheets of homologous repeated sequences within each molecule are aligned in parallel and in pseudo-register. Knowledge of this structure led to a proposal of the molecular mechanism of HET-S toxicity. When HET-S attempts to join the [Het-s] prion aggregate there is a conformational change in the attached non-prion HET-S domain leading to toxicity.

Review 5 (Wickner) describes the structures of other prions. Solid state NMR data for three yeast prions suggest that β-sheets in individual molecules align in parallel and in register. Intriguingly, this structure is shown to explain the finding that an overall QN-rich amino acid composition, rather than a specific sequence, is the essential component of these prion domains. This structure is also shown to be compatible with different heritable conformations of the same protein so it nicely explains the existence of prion strains. This review also considers the central question of whether prions are beneficial to the host or are more appropriately considered disease.

Review 6 (Wolfe and Cyr) argues that although amyloid aggregates are often associated with disease, the aggregates are not the major toxic species. Rather, the toxic species are proposed to be soluble oligomers that appear in the presence of the amyloid aggregate. The unfolded nature of the oligomers may allow them to interact with other cellular proteins in a deadly manner. Amyloid aggregate itself may be cytoprotective if it converts the toxic species into harmless aggregate. Review 7 (Moreno-Gonzalez and Soto) considers the frightening possibility that common protein misfolding diseases such as Alzheimer’s and Parkinson’s may be more similar to prions and more infectious than previously thought.

I would like to thank all the authors for their excellent contributions. I hope these reviews will make the fascinating field of amyloids and prions more accessible to students and scientists in related fields.

References

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