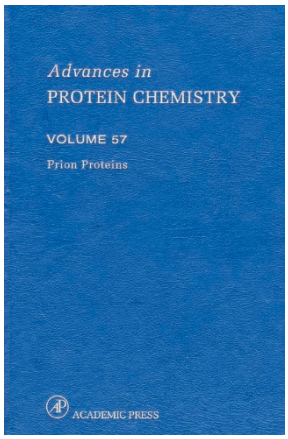
A practical prion protein primer



Advances in Protein Chemistry: Prion Proteins
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Almost two decades have passed since Stanley Prusiner proposed that the transmissible agent causing spongiform encephalopathies consists of a misfolded protein — but the biology of prion diseases is more mesmerizing than ever. Some of the fascination is the result of a curious hiatus: one could argue that prion diseases are the best-understood neurodegenerative diseases, with an impressive wealth of transgenic models for pathogenesis, agent replication and tissue damage. But we still understand very little of the molecular nitty-gritty of prion propagation.

The latter is arguably a problem of protein chemistry and biophysics, which is what Byron Caughey's book addresses. Over 12 chapters, all thinkable aspects of prion-protein biochemistry are dissected, largely by the field's best experts. The book opens with a general introduction of the properties of the prion protein (by Suzette Priola), followed by a few methodological chapters that discuss the application of, for example, mass spectrometry (by Michael Baldwin) and nuclear magnetic resonance (by Kurt Wüthrich) to prion proteins.

The energetics of protein folding is described in an interesting chapter by Rudi Glockshuber that covers, among other topics, the stability of prion proteins carrying mutations linked to human hereditary spongiform encephalopathies. Biophysically challenged readers, however, may be taken aback by the lack of description of specialized methods such as stopped-flow fluorescence. (Refreshingly, the zeitgeist buzzword "proteomics" does not figure prominently in any section of the book.)

Alonso and Daggett discuss the application of computer simulation to the structure of cellular and disease-associated prion proteins. They describe a set of fascinating techniques in accessible language. The authors make the credible point that computational structure simulations are still necessary and useful, even though the structure of the normal prion protein was solved by nuclear magnetic resonance spectroscopy four years ago. But, despite their usefulness, computer simulations have failed to predict the three-helical structure of the cellular prion protein, and it is (in my opinion) questionable whether the 'scrapie' transition discussed in this chapter is related to what happens in the brains of infected animals.

Byron Caughey's own specialty, *in vitro* conversion of the prion protein, is given an exhaustive, but not unduly extensive treatment. The two most popular models of prion propagation, template-directed refolding versus ordered seeded aggregation, are explained with admirable clarity. An array of useful methods for approaching these phenomena is explained with simple flowcharts. Caughey is also very outspoken about the current limitations of the technologies that he has invented, and concludes, on the basis of the substoichiometric yield of prion conversion *in vitro*, that "fundamental mysteries remain about molecular mechanisms of transmissible spongiform encephalopathy (TSE) diseases".

The biogenesis of the cellular prion protein is discussed by David Harris, along with the (few) available cellular models of prion diseases. Somewhat less illuminating is the enumeration of molecules (by Weiss and colleagues) that may interact with the prion protein. Some of these interactions are described at great length although they have not been shown, as far as I know, to be biologically significant: the only molecular complex that may actually accomplish signal transduction, PrP/caveolin/fyn, is mentioned in just four lines.

The book closes with two highly accessible, very well written chapters by Reed Wickner and Susan Lindquist, the inventors of the yeast prion concept. As a mammalian prionologist, I cannot avoid being envious of the breakneck pace of progress in the yeast prion field — which might be because the doubling time of yeast is much shorter than that of mice. In the two cases characterized by Wickner and Lindquist, URE3 and PSI, inducibilty, swappable prion domains, dominant negative moieties, refractory genetic states ("psi no more"), and even *de novo* prion generation *in vitro* have been described, so that Prusiner's protein-only hypothesis stands on much firmer ground in yeast than it does in mammals.

One conspicuous omission is a serious discussion of the function of the normal prion protein. Although this topic is mentioned *en passant* in the chapters on transgenic models of prion diseases (John Collinge) and on PrP receptors (Stefan Weiss), one is almost led to conclude, after digesting the book as a whole, that the prion protein is only there to bestow prion diseases upon us. This unlikely, as the emerging findings about the interplay between PrP and its homologue, Dpl, are beginning to indicate.

In these days of ubiquitous web-based availability of up-to-date review articles, every book on an active field of science faces some existential questions. Because web sites of journals are updated more frequently than books can be possibly reprinted, the content of books can rapidly become stale. Caughey's book is remarkably up-to-date, but — by necessity — fails to discuss the exciting new data on dimeric crystals of the prion protein, as well as the claims that misfolded prion proteins can be amplified cyclically.

Notwithstanding these minor critiques, Caughey's endeavor was largely successful. In general, I enjoyed the book, and have learned quite a few things about modern methods of protein analysis. Investigators with a background in protein chemistry who wish to enter the prion field, as well as prionologists who desire to deepen their knowledge of prion biophysics, will find many aspects of this book stimulating and informative. □

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