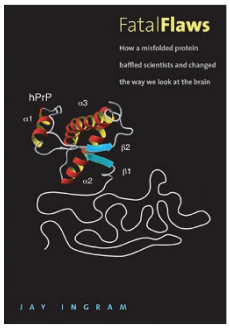
The story of the rogue prions



Fatal Flaws: How a Misfolded Protein Baffled Scientists and Changed the Way We Look at the Brain

Jay Ingram

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Reviewed by Claudio Soto

One of the most intriguing discoveries in modern biology was the finding that proteins can act like microorganisms to transmit disease. In *Fatal Flaws*, Jay Ingram describes the fascinating story behind the infamous prions, the infectious agents responsible for a variety of fatal human and animal neurological diseases.

The book is written in a way that can be easily followed by a non-specialist but that at the same time includes sufficient technical details to fully appreciate the scientific revolution produced by the discovery that proteins can sometimes behave like living organisms. Prions are so mesmerizing because on the one hand they are very simple, yet on the other they exhibit an exquisite complexity. After all, they are thought to be composed exclusively of a misshapen version of a medium-sized and otherwise ordinary protein, without any genetic material. However, they exhibit the complex features of bona fide infectious agents; namely, they can exponentially multiply in an appropriate host, they can transmit between individuals by diverse routes of exposure (including through food, blood and air), they are highly resistant to elimination, they can penetrate biological barriers, they can progressively accumulate and persist in the environment, they can cross species barriers and they can mutate and evolve to give rise to a variety of 'strains' that can produce diseases with substantially different clinical manifestations. Another puzzling contrast in prion biology is that they appear to be extremely efficient infectious agents, yet the number of natural cases of prion transmission, especially in humans, is very small. Indeed, it is possible to split the brain of a prion-infected individual into one billion pieces, and inoculation with just one of them is sufficient to transmit the disease. Also, prions are almost indestructible; it is possible to heat them to boiling temperatures or bury them for years and they remain highly infectious. It is likely that millions of people have been exposed in one manner or another to infectious prions, yet the human forms of prion diseases are very rare.

In the first part of the book, Ingram colorfully relates the story of how these unorthodox infectious agents were first identified and associated with some weird diseases involving accidental transmission, artificial methods of food processing and the practice of cannibalism. He also masterfully describes the birth of the prion hypothesis, the prominent role played by Stanley Prusiner in the identification and characterization of prions and the passionate controversy that surrounded the prion field for three decades. In what may be an attempt to make the book more exciting and easily comprehensible for lay readers, Ingram includes a too-extensive description of the personalities and motivations of the scientists involved and also, in my opinion, too much introductory material about cellular functioning and protein biology. In addition, I believe that he provides too little information about the most recent discoveries that solidified the prion hypothesis and conquered the minds of some of the most skeptical scientists, such as the production of infectious prions in a test tube by inducing or propagating the misfolding of a prion protein that had been artificially synthesized in bacteria.

The book ends by describing recent exciting studies expanding the prion concept towards other neurological diseases. The last decade has been very exciting in the prion field; we have witnessed the almost universal acceptance of the idea that prions are indeed composed mostly of a protein and the simultaneous explosive expansion of the prion principle to explain the molecular mechanism of progression for some of the most prevalent neurological disorders, including Alzheimer's and Parkinson's diseases. One relevant topic that Ingram's book neglects, I believe, is the idea that transmission of biological information through templated propagation of alternative protein conformations, following the prion principle, may actually be a universal phenomenon not restricted exclusively to diseases. This idea started to take shape with the clever experiments performed by Reed Wickner, Susan Lindquist and others showing that some inheritable genetic traits in yeast may be transmitted through protein-based heritable determinants of phenotype. Like mammalian prions, yeast prions are proteins that have acquired an abnormal conformation and propagate by inducing their normal protein counterparts to adopt the same altered conformation. Currently, 'functional prions' have been recognized in various organisms among many different proteins. The number of proteins utilizing the prion mechanism to perform their biological functions is unknown, but the concept that biological information can be transmitted by propagation of protein (mis)folding may revolutionize our understanding of biology.

Despite the fact that prion diseases are extremely rare in humans, the unique biology behind the mechanisms of prion transmission, the heretical nature of the prion as an infectious agent and the potential for dramatic medical and economic consequences arising from prion proteins have put them in the spotlight. This book provides an accessible account of the story behind one of the most intriguing scientific discoveries in modern biology and the contributions of the major players involved. Furthermore, as Ingram points out, the scientific revolution produced by the prion concept is not yet fully realized. It is possible that the unique biology of prions may bring answers for some of the most devastating diseases of our time and lead to a major change in our knowledge of how proteins work in the complex world of the cell.

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