MEDICAL INTELLIGENCE UNIT

Yury O. Chernoff

Protein-Based Inheritance

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Dedication

Dedicated to people who have enough strength and bravery to stand their ground even against a majority of others in the endless pursuit of truth.

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PREFACE

This book covers a topic which has been neglected for years and has come back into the spotlight only recently. Until the genetic role of DNA was firmly established, many researchers suspected that proteins rather than nucleic acids could be carriers of heritable information. However, these models were completely forgotten with the triumphal march of the double helix and development of a central dogma, postulating that information flow occurs strictly from DNA through RNA to protein, making it seemingly impossible for the proteins to possess a coding potential. Proteins were downgraded to the role of simple perpetuators and executors of DNA orders. While it was certainly recognized that protein "serfs" are indispensable for the well-being of their powerful nucleic acid "lords", the thought of a protein occupying a key position in the hereditary hierarchy was as unthinkable in modern molecular genetics as was the peasant's to the king's throne in medieval Europe.

As aspiration frequently occurs in science, data that could not be explained within the framework of a "nucleic acid only" model of heredity existed for years and were just waiting for the proper moment to resurface. Attention to these non-conventional phenomena focused on the transmissible spongiform encephalopathies (TSEs), later termed "prion diseases". Accumulated results led to the model proposing that a TSE infectious agent (prion) is composed of the wrongly shaped protein, capable of converting the normal protein of the same amino acid sequence into a prion shape. As usual, this revolutionary model was not immediately accepted by the scientific community. Yet it has eventually gained recognition, highlighted by a Nobel Prize awarded to S. Prusiner for studying prion diseases in 1997. Despite this, some researchers remain skeptical in regard to the "protein only" nature of the TSE agent even today. Mammalian prion diseases were covered in great detail in some recent books (for example, *Prion Biology and Diseases* Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 2004, edited by S. Prusiner, and *Prions and Prion Diseases: Current Perspectives*, Horizon Scientific Press, 2004, edited by G. Telling). Although transmission of mammalian prions from one organism to another represents infection rather than inheritance, the ability of a protein to act as an information carrier, postulated in the prion model of TSEs, certainly paved the way for acceptance of such a role in heredity for at least some proteins.

Application of the prion model to some yeast non-Mendelian elements was introduced by R. Wickner in 1994 and confirmed by further research in various labs. Prions of yeast and other fungi manifest themselves as protein-based heritable elements, thus demonstrating that proteins may serve as carriers of hereditary information. Most fungal prions are heritable amyloids (that is, ordered fibrous aggregates) propagated by nucleated polymerization, that is similar to a mechanism proposed for mammalian prion diseases. Moreover, recent advances leave no doubts that patterns of the fungal prions are

controlled and reproduced exclusively at the protein level. Prion (or prion-like) phenomena based on self-activating protease and possible self-activating kinase were also described. In principle, prion inheritance does not contradict the central dogma as DNA still remains needed for initial protein production. However, prion transmission in generations clearly shows that changes occurring at the protein level can become reproducible and heritable without any corresponding change occurring in DNA sequence. Heritable prions essentially meet all the criteria of non-Mendelian genes that were in use during the classic genetics era. Connection between mammalian and fungal prions, as well as genesis of the yeast prion concept and some structural and biological implications drawn from recent studies of fungal prions are described by R. Wickner and coauthors in Chapter 1.

The prion model provides a molecular basis for some fungal non-Mendelian phenomena that were studied for years but were not be understood within the framework of conventional concepts. Chapters 2 (by M. Tuite and B. Cox) and 3 (by S. Saupe) provide a comprehensive description of two such phenomena, respectively [*PSI*$^+$] of *Saccharomyces cerevisiae* and [Het-s] of *Podospora anserina*, with inclusion of both historical recollections and current data explaining the mechanisms of previously observed patterns. Studying various combinations of the amyloid-based prions in yeast uncovered complex interactions between them, in some cases leading to generation of prion "cascades", where pre-existing prion facilitates de novo formation of the prion isoform of an unrelated protein. These and other types of prion-prion interactions are described in Chapter 4 by S. Liebman and I. Derkatch.

Although most of the known prions (that is, infectious or heritable proteins) are amyloids, there are other amyloids (including those associated with important human diseases) which do not possess prion properties. Specific features of the yeast prion proteins, that make these proteins capable of propagating the prion state and distinguish them from non-heritable amyloids, are considered in Chapters 5 (by B. Cox and coauthors) and 6 (by M. Ter-Avanesyan and coauthors). A crucial distinction is a pattern of interactions between the amyloid aggregates and certain chaperone proteins that play a major role in propagation of yeast prions in vivo. Chapter 7 (by E. Rikhvanov and coauthors) compares the effects of chaperones on prion and non-prion aggregates, concluding that these effects are based on the same molecular mechanisms, but lead to different consequences depending on the nature of the protein substrates. As a result, the chaperone machinery designed to protect cells from protein aggregates is turned by a prion into a tool for propagation of prion aggregates.

Despite a significant amount of information accumulated during recent years, the biological role of prion phenomena remains a matter of extensive discussions. Chapter 8 (by S. Inge-Vechtomov and coauthors) considers potential biological roles of prion domains in detail, describing both the pathological and potentially adaptive effects of amyloid formation and pointing to mechanisms that may govern the evolution of prion-forming sequences.

While fungal prions surely represent the most extensively studied example of protein-based inheritance, it is not the only example known to date. Ironically, the oldest proven case of the hereditary change which does not involve DNA is almost as old as the DNA-centered concept of inheritance. This first evidence for protein-based inheritance has come from research in Protozoa, specifically in ciliates, where it has been shown that a surgically produced alteration of the complex multiprotein structure becomes heritable in a template-like fashion. This eventually led to development of the "structural templating" concept, also applicable to prion phenomena. These and other data on the inheritance of preformed structures in Protozoa are considered in Chapter 9, written by one of the pioneers of this research, J. Beisson.

Finally, Chapter 10 by P. Wilson deals with the long debated phenomenon of centrosome inheritance which was considered as a potential example of non-chromosomal templating. Even though recent data do not support protein-based templating being involved in the centrosome reproduction, they certainly reveal certain effects of pre-existing structures on the formation of new centrosomes during cell division. Examples described in Chapters 9 and 10 touch on "the chicken and the egg" issue...the origin and reproduction of the eukaryotic cytoskeletal structures in general, a matter that is far from being solved.

Taken together, data included in this book prove beyond a reasonable doubt that proteins and multiprotein complexes are able to control heritable traits, and that at least in some examples, this control occurs in a template-like fashion, so that new structures strictly reproduce patterns of pre-existing structures that were not specifically coded in DNA. Thus, protein-based inheritance has left the area of speculation and has emerged as a new topic amenable to high-quality experimental analysis. Nucleic acid lords will no longer be capable of disregarding the contributions of their protein serfs to the overall heritable composition of the cell and organism. Moreover, connections between the mechanisms of protein-based heritable phenomena and some important diseases (such as Alzheimer's disease and other disorders related to amyloid formation) make it probable that protein-based inheritance will attract even more attention in the near future.

Certainly this book represents only the tip of the iceberg, and its composition is biased due to both the state of the field at the moment and the preferences of the editor, that can never be put aside completely, no matter how hard one tries to do so. If presentation of the proven cases of protein-based inheritance weakens the natural "DNA chauvinism" of the readers, while discussion of emerging speculations leads some researchers to explore alternative explanations of the other mysterious phenomena, then I could conclude that the book has played its role as intended. This is not to say that knowledge of DNA sequences of everyone and everything is unimportant. This is just to note that it may not be enough. And while exact

knowledge of the firmly established facts is certainly rewarding, this is a call of the unknown that always drives science forward.

Remaining fascinated and obsessed with this call, and being grateful beyond words to the great team of authors who actually wrote this book, I offer the product of our work to the readers.

Yury O. Chernoff, Ph.D.

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