

Preface

The goal of protein structural biology has been the determination of the relationship between structure and function. How do polypeptide chains leaving the ribosome fold to produce functional enzymes, structural proteins, peptide hormones, etc.? Once folded, how do these proteins perform their functions? What are the structures of the active sites of enzymes and how do they catalyze chemical reactions? For biochemists of a certain age (old), an intrinsic assumption in such questions is that nascent proteins fold into *stable* three-dimensional structures. After all, how can an enzyme, for example, catalyze a reaction if it is unstructured? This transition from nascent polypeptide to native protein was viewed as a binary process—unfolded $\leftrightarrow$ folded. No doubt Anfinsen's famous experiments on the unfolding and refolding of bovine pancreatic ribonuclease supported this view.¹ However, with the development of new methods to study not only static protein structure but conformational dynamics as well, it became clear that many regions of the entire conformational space of a protein were populated at relatively high frequencies. These regions corresponded not only to native states but also to partially or fully disordered states. When the functions of the respective proteins were studied, scientists realized that some of these were performed by nonnative state conformers. Folding and function no longer depended solely on the binary process unfolded $\rightarrow$ folded, but often *required* partially folded or unfolded states. Thus, as Uversky describes in Chapter 1 of this volume, "instead of the classical protein structure-function paradigm rooted in the 'one-gene – one-protein – one-function' model, a correlation between protein structure and function is described by a more general 'protein structure-function continuum' model." This continuum includes proteins without native folds as well as proteins in which both ordered and disordered regions exist. This latter group of proteins has been classified as "intrinsically disordered proteins" (IDPs) and the 10 chapters in this volume provide the reader an introduction to, and an exposition of, this dynamic protein class.

Vladimir Uversky, the volume editor, begins with a broad introduction to the field, discussing, among other things, thermodynamic properties of IDPs, subclasses of IDPs (there are many) and their functions, and how the classical gene $\rightarrow$ polypeptide $\rightarrow$ unique structure model has been supplanted by models in which a single gene can produce a number of polypeptide chains,

some of which may have unique structures but others of which may exist within a conformational ensemble. Subsequent chapters discuss specific subclasses of IDPs. These include IDPs involved in normal cellular protein-protein interactions (14-3-3 proteins), formation and function of the sarcomere (the basic unit of striated muscles), regulation of transcription (hypoxia-inducible factor 1 α), and formation of functional and pathologic amyloids. Two chapters discuss how IDPs are involved in diseases, including prostate and ovarian cancer and Alzheimer's and Parkinson's disease. The involvement of IDPs in such a broad range of normal and disease states highlights the potential of computational methods of predicting the functions of regions of disorder directly from protein sequences. Katuwawala et al. discuss a comprehensive collection of 25 computational methods for doing so. A final chapter discusses methods to determine ensemble-averaged hydrodynamic radii of IDPs as a probe of their structure.

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Reference

1. Anfinsen CB. Principles that govern the folding of protein chains. *Science*. 1973; 181:223-230.