Fuzziness: Structural Disorder in Protein Complexes

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FUZZINESS: STRUCTURAL DISORDER IN PROTEIN COMPLEXES
Monika Fuxreiter and Peter Tompa

Fuzziness

Structural Disorder in Protein Complexes

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Springer Science+Business Media, LLC

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Springer Science+Business Media, LLC
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Springer Science+Business Media, LLC, 233 Spring Street, New York, New York 10013, USA
http://www.springer.com

Please address all inquiries to the publishers:
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Phone: 512/ 637 6050; FAX: 512/ 637 6079
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The chapters in this book are available in the Madame Curie Bioscience Database.
http://www.landesbioscience.com/curie

Fuzziness: Structural Disorder in Protein Complexes, edited by Monika Fuxreiter and Peter Tompa. Landes Bioscience / Springer Science+Business Media, LLC dual imprint / Springer series: Advances in Experimental Medicine and Biology.

ISBN: 978-1-4614-0658-7

Library of Congress Cataloging-in-Publication Data

Fuzziness : structural disorder in protein complexes / edited by Monika Fuxreiter, Peter Tompa.
p. ; cm. -- (Advances in experimental medicine and biology ; no. 725)
Includes bibliographical references and index.
ISBN 978-1-4614-0658-7
1. Proteins--Conformation. 2. Protein folding. 3. Protein binding. 4. Fuzzy systems. I. Fuxreiter, Monika, 1969- II. Tompa, Peter. III. Series: Advances in experimental medicine and biology ; no. 725. 0065-2598
[DNLM: 1. Protein Conformation. 2. Protein Denaturation. QU 55.9]
QP551.F99 2011
572'.633--dc23

2011021158

DEDICATION

To our future generation

FOREWORD

For more than 40 years following the determination of the first protein structure, molecular biology was guided by two central dogmas which posited that the ordered three dimensional structure of a protein is intimately linked to its biological function and that binding of a protein to ligands or to other protein molecules is exquisitely specific. It therefore came as a surprise when, in the latter half of the 1990s, experimental work on several regulatory proteins and bioinformatics surveys performed on a genomic scale showed that regions of conformational disorder are common in eukaryotic proteins involved in cellular regulation and signaling. Such intrinsically disordered proteins (IDPs) frequently function as central hubs in protein interaction networks, binding multiple protein partners. IDPs often contain short amphipathic motifs that fold into ordered structures upon binding to their targets. However, in many cases, the IDP remains disordered even in the bound state—a phenomenon aptly named "fuzziness" by Peter Tompa and Monika Fuxreiter, the editors of this volume.

Detailed characterization of fuzzy interactions will be of central importance for understanding the diverse biological functions of intrinsically disordered proteins in complex eukaryotic signaling networks. In this volume, Peter Tompa and Monika Fuxreiter have assembled a series of papers that address the issue of fuzziness in molecular interactions. These papers provide a broad overview of the phenomenon of fuzziness and provide compelling examples of the central role played by fuzzy interactions in regulation of cellular signaling processes and in viral infectivity. These contributions summarize the current state of knowledge in this new field and will undoubtedly stimulate future research that will further advance our understanding of fuzziness and its role in biomolecular interactions.

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PREFACE

For almost four decades proteins were thought to function as entities with well-defined structures, and to each biological task a unique conformation was assigned. A decade ago it was recognized however, that some proteins do not obey this rule and act as a heterogeneous ensemble of conformations. These proteins were termed as intrinsically unstructured or intrinsically disordered proteins (IUPs or IDPs). IDPs brought a new flash into structural biology urging to change our deterministic one sequence-one structure-one function concept to a one sequence-multiple structures-one function paradigm. Many IDPs serve in molecular recognition processes, and upon targeting different partners they often adopt a well-defined three-dimensional structure. It gives the impression that although IDPs have extensive conformational freedom in the unbound state in solution they behave as 'regular' proteins upon fulfilling their functions. This view however, is misleading. The structured image of bound IDPs only reflects experimental difficulties in characterizing conformational ensembles of complexes. Indeed, many parts of IDPs preserve their structural heterogeneity even upon interacting with other molecules. Some biochemical studies demonstrate that these parts often coincide with functionally critical regions. The two statements together signify that structural disorder in complexes is important for various biological roles. This phenomenon is termed fuzziness. Structural ambiguity in complexes expands the capacity of proteins to perform multiple functions and also provides an additional level of versatility for regulation. The existence of fuzzy complexes calls for the ultimate reassessment of the classical one structure-one function paradigm and converts it to a one sequence-multiple structures-multiple functions paradigm. This book is dedicated to this new concept and via many examples introduces a new view on protein functionality.

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ABOUT THE EDITORS...

MONIKA FUXREITER is a senior scientist at the Institute of Enzymology, Hungarian Academy of Sciences in Budapest, Hungary and a visiting scientist at the Weizmann Institute of Science, in Rehovot, Israel. Her main interest is to develop mechanistic models for proteins, especially structure-function relationships for intrinsically disordered proteins and their complexes. She also studies the role of dynamism in protein evolution. She often shares ideas with her children, Krisztina and Pal. Monika Fuxreiter received her degrees from the Eötvös Loránd University, Budapest, Hungary.

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PETER TOMPA is a professor of protein sciences at the Institute of Enzymology of the Hungarian Academy of Sciences, Budapest, Hungary. His interest focuses on the structural disorder of proteins, a phenomenon that defies the classical structure-function paradigm of proteins that is about to change our general concepts of protein structure and function. He made basic contributions to this field, he organized the first international meeting dedicated to this topic in 2007 and wrote the first monograph on structural disorder (Structure and function of intrinsically disordered proteins, 2009, CRC Press, a Taylor and Francis group, Boca Raton, FL, USA). He has published over 100 papers in international journals and holds a DSc degree from the Hungarian Academy of Sciences. Recently he took the position of director at the VIB Department of Structural Biology, Brussels, Belgium.

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