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FUZZINESS: STRUCTURAL DISORDER IN PROTEIN COMPLEXES

Monika Fuxreiter and Peter Tompa

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Fuzziness

Structural Disorder in Protein Complexes

Edited by

Monika Fuxreiter, PhD

*Institute of Enzymology, Biological Research Center, Hungarian Academy of Sciences,
Budapest, Hungary*

Peter Tompa, PhD

*Institute of Enzymology, Biological Research Center, Hungarian Academy of Sciences,
Budapest, Hungary*

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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.

*Peter Wright, PhD
Department of Molecular Biology and
Skaggs Institute for Chemical Biology
The Scripps Research Institute
La Jolla, California, USA*

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.

Monika Fuxreiter, PhD

Peter Tompa, PhD

*Institute of Enzymology, Biological Research Center
Hungarian Academy of Sciences, Budapest, Hungary*

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.

ABOUT THE EDITORS...



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.

PARTICIPANTS

Sarah E. Bondos
Department of Molecular
and Cellular Medicine
Texas A&M Health Science Center
College Station, Texas
USA

Jean-Luc Darlix
LaboRetro
Unité de Virologie Humaine
INSERM 758,
IFR 128, ENS de Lyon
Lyon
France

Ariele Viacava Follis
Department of Structural Biology
St. Jude Children's Research Hospital
Memphis, Tennessee
USA

Monika Fuxreiter
Institute of Enzymology
Biological Research Center
Hungarian Academy of Sciences
Budapest
Hungary

Charles A. Galea
Structural Biology Division
Walter and Eliza Hall Institute
of Medical Research
Parkville
Australia

Jeffrey C. Hansen
Department of Biochemistry
and Molecular Biology
Colorado State University
Fort Collins, Colorado
USA

Hao-Ching Hsiao
Department of Molecular
and Cellular Medicine
Texas A&M Health Science Center
College Station, Texas
USA

Roland Ivanyi-Nagy
Molecular Parasitology Group
The Weatherall Institute
of Molecular Medicine
University of Oxford
Oxford
UK

Elizabeth A. Komives
Department of Chemistry
and Biochemistry
University of California San Diego
San Diego, California
USA

Richard W. Kriwacki
Department of Structural Biology
St. Jude Children's Research Hospital
and
Department of Molecular Sciences
University of Tennessee Health
Sciences Center
Memphis, Tennessee
USA

Kevin A.W. Lee
Department of Biology
Hong Kong University of Science
and Technology
Hong Kong
China

Sonia Longhi
Architecture et Fonction des
Macromolécules Biologiques
Universités d'Aix-Marseille I et II
Marseille
France

Steven J. McBryant
Department of Biochemistry
and Molecular Biology
Colorado State University
Fort Collins, Colorado
USA

Régis Pomès
Molecular Structure and Function
Hospital for Sick Children
and
Department of Biochemistry
University of Toronto
Toronto
Canada

Sarah Rauscher
Molecular Structure and Function
Hospital for Sick Children
and
Department of Biochemistry
University of Toronto
Toronto
Canada

Alexander B. Sigalov
SignaBlok, Inc.
Shrewsbury, Massachusetts
USA

Peter Tompa
Institute of Enzymology
Biological Research Center
Hungarian Academy of Sciences
Budapest
Hungary

G. Rickey Welch
Department of Biological Sciences
and Department of History
University of Maryland
Baltimore, Maryland
USA

Peter Wright, PhD
Department of Molecular Biology
and
Skaggs Institute for Chemical Biology
The Scripps Research Institute
La Jolla, California
USA

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