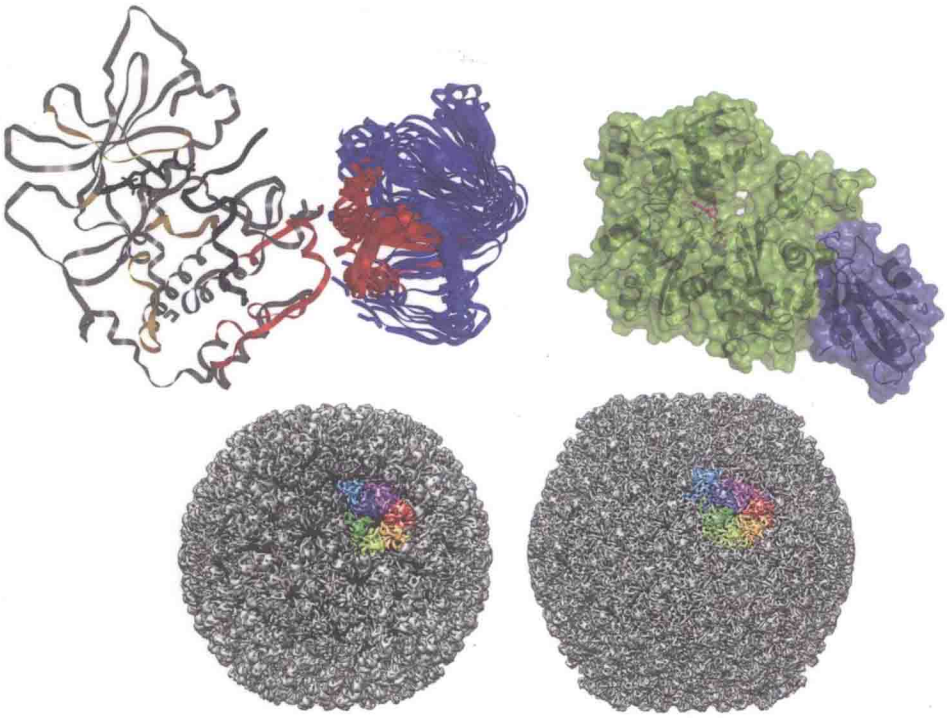
Mass Spectrometry Analysis for Protein-Protein Interactions and Dynamics

Edited by
Mark Chance



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FOREWORD

This book would not have been possible without the efforts of scientists in the field who have labored to advance the field of structural mass spectrometry over the last several years. These efforts, and the germ of an idea that a book such as this was timely and possible, came together in January 2006 in the form of a mass spectrometry meeting, the 18th Sanibel Conference on Mass Spectrometry, titled "Focus on Biomolecular Structure, Dynamics and Function: Hydrogen Exchange and Covalent Labeling Techniques", organized by Igor Kaltashov and John Engen. At this three-day meeting, experts in mass spectrometry, many of which are authors of chapters in this book, exchanged the latest ideas related to understanding protein structure and dynamics, and found that mass spectrometry based approaches were converging on a common goal: to fill gaps in our understanding of protein structure and conformational dynamics, built on a firm foundation of high resolution structure data.

This group has since that time strengthened their interactions, forming a Hydrogen Exchange and Covalent Labeling interest group within the American Society for Mass Spectrometry; this group has grown in two short years to over 750 members. This book provides a milestone in the efforts of this group to present the state-of-the art in their field and disseminate that art as widely as possible. The future of this field looks very bright indeed.

On a personal note, I wish to thank all of my co-authors, I earnestly hope they find their efforts to be rewarded in this volume. I also wish to acknowledge the outstanding editing assistance from Shannon Swiatkowski and the support of all the faculty and staff of the Case Center for Proteomics, whose single minded pursuit of excellence makes being Center director a very rewarding occupation.

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Cleveland, Ohio
May 2008

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CONTENTS

CHAPTER 1

Overview of Mass Spectrometry Technologies for Examining Protein Structure: Current and Future Directions

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1.1 INTRODUCTION

Understanding the molecular structure and dynamics of macromolecules at high resolution and with high throughput is a topic of great importance in biology. Nuclear magnetic resonance (NMR) and crystallographic approaches are the foundation of rapid progress in this area. Access to genome sequences and cloning resources from an ever-increasing number of organisms and allied high-throughput structure and modeling studies are likely to enable resolution of the structure of most protein domains in the near future (Chance et al., 2004). However, the machinery of eukaryotic cell biology involves multidomain proteins that interact in large complexes as molecular machines (Sali et al., 2003; Russell et al., 2004). Understanding how these domains interact is crucial in understanding their function. As this "database" of structural information evolves and develops, examination of the structure–function relationships of a wide range of proteins becomes possible. In addition, many biological questions of interest invoke questions of protein dynamics, ligand binding, complex formation, or the structural effects of posttranslational modifications. Many of these experiments are beyond the range of classical structural biology approaches (see below) and structural mass spectrometry (MS) methods have been very successful in filling this technological gap. The fundamental contributions of mass spectrometry to structural biology studies have grown dramatically due to increases in instrument sensitivity and resolution that have accrued over the past 10 years. This has advanced our ability to reliably sequence and identify protein

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fragments and their modified products, a feature on which structural mass spectrometry fundamentally relies. This book catalogs the state of the art in these approaches and provides a perspective on the future prospects for the field. The three main technologies of structural mass spectrometry that have rapidly evolved and grown, include covalent labeling strategies, hydrogen–deuterium (H/D) exchange, and chemical cross-linking.

Although the technologies have a great many differences in their sample preparation, instrumentation requirements, and other details of the approaches, their similarities must not be overlooked. First, they all rely on detailed identification and sequencing of peptide fragments generated by specific or nonspecific cleavage of intact and (generally) purified protein species (or complexes). Second, they infer structural information based on a mass shift of these peptide species after exposure to the labeling reagents of choice. The target atoms that are labeled must be solvent accessible, at least transiently. Third, the value of the structural information is greatly enhanced by having a structural model of the protein or proteins. It is, in fact, very clear that the advancement of these approaches will be significantly accelerated by a union of these experimental technologies with computational modeling approaches in the context of the rapidly expanding structure databases (Chance et al., 1997; Guan et al., 2004; Kamal and Chance, 2008; Takamoto and Chance, 2006).

Structural models for most protein domains, providing a foundation for structural mass spectrometry, are accumulating rapidly (Eswar et al., 2007). Advances in protein structure determination and computational modeling mediated by structural genomic initiatives throughout the world promise to correlate sequence and structure for most protein domains within the next 5 years (Burley et al., 1999; Chance et al., 2002, 2004). Coincident with progress toward this milestone is the realization of the importance of macromolecular interactions and even the fundamental significance of large macromolecular complexes mediating most normal and aberrant biological functions (Gavin, 2005). Solving the structure and connecting it to function for these large complexes are two of the most important challenges in structural biology today. Unlike solving the structure of protein domains or short nucleic acids that contain tertiary structure, this effort is far from high throughput and likely involves a combination of computational and experimental approaches, tailored specifically to the problem at hand.

The barriers to determining the structure and dynamics of proteins and their complexes include known limitations in crystallography and NMR technologies. Issues such as complex size, crystallizability, solubility, and amounts of materials are well known. In recent years, electron microscopy (EM) and tomography techniques, particularly at low temperatures, have substantially improved and are making important contributions to determining the structure of complexes (Sali et al., 2003). These approaches have resolution limitations for many samples and are better for larger complexes or cells due to sample dose tissues. This leaves a gap in technological progress for the "medium" size complexes, particularly medium-sized binary complexes (50–200 kDa). This has spurred the development of a host of computational methods that can fill in the gap and contribute to understanding the relationship between protein structure and function.