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Methods and Protocols

Edited by

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Humana Press

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Preface

Recent progress in experimental techniques has led to a revolutionary change in life science research. High-throughput genome sequencing and assembly techniques, together with new information resources, such as structural and functional proteomics, transcriptome data from microarray analyses, or light microscopy images of living cells, have led to a rapid increase in the amount of data available, ranging from complete genome sequences to cellular, structure, phenotype, and other types of biologically relevant information. As a consequence, novel system-level studies are now being performed with the goal of understanding and predicting the behavior of complex systems, such as cells, tissues, organs, and even whole organisms. The field of proteomics plays an essential role in this new systems approach to molecular and cellular studies by identifying the genes involved and determining their functional significance; this makes it possible to understand the complex functional networks and control mechanisms that govern the system's response to perturbations, such as environmental changes or genetic mutations.

Research in the emerging field of proteomics is growing at an extremely rapid rate. The real challenge is the relative quantification of proteins, targeted by their function. Mass spectrometry-based strategies were developed to identify modifications in the proteome profile in correlation with functional changes. In practice, the task involves the identification of peptides in a peptide mixture of extremely high complexity. This identification and relative quantification will allow researchers to study changes in the level of expression, in the processing, or in the post translational modifications of a set of proteins. Recent technical innovations in mass spectrometry-based techniques have resulted in a range of highly sensitive and versatile instruments for high-throughput, high-sensitivity, proteome-scale profiling and the door is now open for a wide range of applications exploiting these approaches. But mass spectrometry is only one among many other techniques that are part of an analytical strategy. These alternative or complementary technologies include two-dimensional gel electrophoresis, protein microarrays, yeast two-hybrid systems, phage display, and immunoprecipitation. However, there is no one technology of choice and the most appropriate method will depend on the size and the nature of the system being studied and the type of results desired. The principal aim of this volume is to describe the latest protocols being developed to address the problems encountered in high-throughput proteomics projects, with emphasis on the factors governing the technical choices for a given application. The volume is aimed at researchers

working in the field of proteomics including chemical engineers, analytical chemists, biochemists, cell and molecular biologists, clinical scientists, and bioinformaticians, as well as those who are contemplating using proteomics for functional studies.

In functional proteomics, successful characterization of proteins from mass spectrometry experimental data will depend on the technological choices made during the three main phases of the study:

1. The strategy used for the selection, purification, and preparation of the sample to be analyzed by mass spectrometry.
2. The type of mass spectrometer used and the type of data to be obtained from it.
3. The method used for the interpretation of the mass spectrometry data and the search engine used for the identification of the proteins in the different types of sequence data banks available.

The mass spectrometry part itself is often seen as the most important one because it corresponds to the largest budget. It is also time consuming, being very complex and highly technical. Nevertheless, the sample preparation and the data analysis steps are equally important, if not more important, for the success of a proteomic experiment. Therefore, in this volume, the case studies presented will always insist on the three aspects of the experimental design. In the initial chapters, different mass spectrometry instrumentation will be introduced in the context of various applications, from the study of large multiple protein complexes to complete organism proteomics. The advantages and the best use of the following types of instruments will be discussed: MALDI-TOF for simple mass finger printing protein identifications as well as MALDI-TOF-TOF, LC-MALDI-TOF-TOF, and LC-ESI-MS-MS (at low, average, and high resolution), detailing the characteristics and capabilities of the different types of mass spectrometers in term of sensitivity, resolution, accuracy, and MS-MS. Metabolomic studies, which are also experimentally based on mass spectrometry, will also be presented, since metabolomic changes obviously reveal functional changes. The following chapters describe the use of mass spectrometry for the detection of protein–protein specific interactions and posttranslational modifications.

High-throughput proteomics studies generate huge volumes of data, including gel images, mass spectrometry spectra, and protein identifications. These data have to be collected, stored, organized, and interpreted if they are to be used effectively. Bioinformatics plays an important role by providing common data representation standards to enable the comparison and transfer of information between different systems and laboratories. The last chapters of this volume are therefore dedicated to the most widely used database resources, as well as the new computational techniques being developed to search and analyze proteomic data. Finally, emerging computational systems biology methods are described

for the integration of data from multiple sources, in order to model complex structures such as protein networks or regulatory pathways and their response to external perturbations.

Julie D. Thompson
Christine Schaeffer-Reiss
Marius Ueffing

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