Preface

Molecular chaperones are a fundamental group of proteins that are key components of protein quality machinery in the cell. This machinery insures that the folding process of any newly synthesized polypeptide chain results in the formation of a properly folded protein and that the folded protein is maintained in an active conformation throughout its functional lifetime. Molecular chaperones have been shown to play essential roles in cell viability under both normal and stress conditions. Chaperones can also assist in the unfolding and degradation of misfolded or regulatory proteins and in the disaggregation of preformed protein aggregates. Chaperones are involved in other cellular functions including protein translocation across membranes, vesicle fusion events, and protein secretion. As a result, there is a growing interest in the role of molecular chaperones in several diseases including cancers.

In recent years, tremendous advances have been made in our understanding of the biology, biochemistry, and biophysics of function of molecular chaperones. In addition, recent technical developments in the fields of proteomics and genomics allowed us to obtain a global view of the chaperone interaction networks.

This book aims at providing a comprehensive analysis of the function of the diverse systems of molecular chaperones and their role in cell stress responses from a global network perspective. The book is divided into eight main parts that highlight network-based analyses of different chaperone systems. The parts trace the role of chaperones at different stages of the protein's lifetime in the cell from its initial translation on the ribosome to its eventual degradation.

In the Part I, a global view of the chaperone network in yeast is presented. Several high-throughput studies were combined with novel computational approaches to eventually provide an in silico assessment of the workload on chaperones in the cell. This allowed for the determination of the flux of substrates through different chaperone systems. Such an analysis brings us closer to understanding the rules that govern cellular protein homeostasis.

In the Part II, a detailed analysis is provided of ribosome-associated chaperones that assist in the folding of newly synthesized nascent chains as they emerge out of the ribosome. These chaperones include trigger factor in bacteria and NAC and RAC chaperone systems in eukaryotes. Trigger factor has been found to have a

larger substrate repertoire compared to NAC and RAC, which seem to be more selective.

In Part III, a comprehensive overview is given of the Hsp70 and Hsp40 chaperones. Hsp70, Hsp40, and nucleotide exchange factors form what is known as the Hsp70 chaperone system that typically engages with proteins in their extended state and promotes their folding to the native state. This system is highly adaptable and can form varied interaction networks. As a result, this system functions in many cellular pathways in addition to protein folding including protein transport, iron-sulfur cluster assembly, and amyloid formation. The Hsp70 network has been found to belong to the scale free category with a limited number of nodes having a large number of links.

In Part IV, the Hsp90 interaction networks are discussed and explained. The importance of the Hsp90 system stems from the finding that this chaperone is a novel anticancer drug target with several Hsp90 inhibitors currently in clinical trials. Hence, many academic groups and biotech companies are very keen to understand Hsp90 mechanism of function and its interaction network. Several high-throughput proteomics methods have been used in baker's yeast, mammalian cells, and other model organisms such as *Candida albicans* to specifically elucidate this network and how the network changes under different stress conditions and between species. These efforts have also been driven by the development of first- and second-generation Hsp90 inhibitors to be used to combat cancer as well as fungal infections.

In Part V, the interaction network of p23 is discussed. p23 is a highly conserved molecular chaperone that also functions as an Hsp90 cofactor. p23 is involved in a variety of cellular pathways including chromatin remodeling, protein folding, and protein transport. By applying both genetic and physical high-throughput methods, a large number (about 350) of p23 interactors have been elucidated clearly supporting a broad function of this chaperone beyond its role with Hsp90.

In Part VI, the role of chaperones and their interaction networks in different cellular compartments is addressed. In the endoplasmic reticulum (ER), the entry, oxidative folding, and conformational quality control of proteins is maintained by many chaperones and their cofactors. Furthermore, proteins that fail to fold properly are targeted for degradation via the ER-associated degradation (ERAD) pathway that extracts proteins from the ER for eventual degradation by the proteasome in the cytoplasm. Chaperones also play critical roles in the import of proteins into the mitochondria and in maintaining mitochondrial protein homeostasis. The Hsp70, Hsp40, and AAA+ chaperones together with several ATP-dependent proteases are critical in these activities. The network analyses of both ER and mitochondrial chaperones provide important insights into the crosstalk between different chaperone systems that eventually determines protein fate.

In Part VII, a global view is provided of protein degradation from the perspective of the proteasome and ubiquitylation. Many specialized chaperones are required to bring together and properly assemble the ~33 subunits that make up the proteasome. Furthermore, the application of classical proteomic approaches as well as new systems-wide methodologies allowed for the identification of numerous ubiquitylated proteins and ubiquitylation sites. These studies provided a global under-

standing of the ubiquitin-proteasome system and what is termed the ubiquitin code. This is particularly important since the impairment of this system has been associated with many neurodegenerative diseases.

In the last part of this book, Part VIII, chaperone and protease networks in model bacteria and parasites, namely *Escherichia coli*, *Mycobacteria*, *Plasmodium*, and *Leishmania*, are discussed. The chapters in this part highlight several novel aspects as relates to the methodologies used and the biological insights gained. These include the application of a novel high-throughput proteomic method to study the role of chaperones in the prevention of protein aggregation in *E. coli*, the discovery of a new prokaryotic ubiquitin-like protein (Pup) modification system to target proteins for degradation in *Mycobacteria*, and the determination of the role of chaperones and their interaction networks in cell cycle progression in *Plasmodium* and *Leishmania*.

In conclusion, the results and insights presented in this book are the products of the tremendous efforts of many groups whose research is aimed at answering the fundamental basic question of how molecular chaperones and proteases maintain protein homeostasis in the cell. Answering such a question at the molecular level will not be an easy task and will require the use of multiple different approaches. The application of high-throughput methods is but one such approach, albeit a very powerful one.

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