Preface

PROTEIN HOMEOSTASIS, OR PROTEOSTASIS, refers to the concept that there are a variety of highly interactive pathways within cells that control the entire life cycle of the proteome and its complex functions. The field began with the discovery of the heat shock response and the molecular cloning of heat shock genes, and rapid progress was propelled by the demonstration that heat shock proteins function as molecular chaperones to enable, and in some cases accelerate, protein folding and protein assembly. Moreover, there was the recognition that nascent polypeptides could be extremely sensitive to perturbations in their synthesis and folding and consequently were at risk for misfolding and aggregation. These observations led to the development of the proteostasis concept and the idea of a proteostasis network, which serves as an organizing framework for the study of cellular protein quality control. The proteostasis network can be viewed as the sum of the interacting and competing pathways managing proteostasis, which function optimally at the organismal level to determine health but tend to fail in aging and when challenged by stress and degenerative diseases.

Understanding proteostasis is an exciting adventure at the interface of biology, chemistry, and medicine that brings together scientists with diverse backgrounds who are interested in fundamental questions regarding all aspects of a protein’s cellular life cycle, including synthesis, folding, transport, regulation of function, and clearance. The physical–chemical attributes that allow client proteins to interact with the proteostasis network define the research of some investigators, whereas other investigators are interested in how the thousands of macromolecular components of the proteostasis network function as competitive and interacting pathways. Studies have been performed using a wide range of approaches, including in vitro evaluations with specific protein clients and purified molecular chaperones as well as experiments in cellular and organismal models that examine the signaling pathways that regulate the capacity of the proteostasis network and the mechanisms of non-cell-autonomous proteostasis regulation between tissues and organs. Proteostasis failure and cellular dysfunction in humans are closely associated with the large class of protein conformational diseases, including Alzheimer’s disease, Parkinson’s disease, amyotrophic lateral sclerosis, Huntington’s disease, cystic fibrosis, and diseases affecting muscle function, immunity, and metabolism. Therefore, a third group of researchers is interested in understanding how mutations in proteins or alterations in the proteostasis network lead to either loss-of-function or toxic gain-of-function diseases and how cells attempt to ameliorate these maladies by adapting the proteostasis network.

The story of protein homeostasis has been told over a period of 37 years by Cold Spring Harbor Laboratory Press. This has been an inspiring adventure of curiosity-driven science motivated by the use of cell stress as a tool to provoke biological systems to reveal their secrets. The first international heat shock meeting in 1982 was held at Cold Spring Harbor Laboratory, 20 years after the seminal discovery by Ritossa (1962) of an unexpected pattern of chromosome puffs induced by exposing Drosophila third instar larvae to temperature shock. The meeting was accompanied in the same year by Heat Shock: From Bacteria to Man (Schlesinger 1982), which described how cells from diverse species responded to acute heat shock stress by the de novo synthesis of heat shock proteins, suggesting a highly conserved response among all organisms. By the time Stress Proteins in Biology and Medicine (Morimoto et al. 1990) was published, it was abundantly clear that these heat shock proteins induced by heat shock stress were also induced by exposure of cells to a wide range of stress conditions, including heavy metals, oxidants, infection, and various small molecules. Foreshadowing the critical importance of heat shock proteins in protein biogenesis were articles on development and stress
survival. Although the function of heat shock proteins in disease was not yet apparent, there was increasing evidence for heat shock proteins in fever, cancer, and infectious diseases.

Within a few years, it was evident that the primary role for heat shock proteins was to serve as molecular chaperones essential for protein folding, protein translocation, and the biogenesis of mitochondria and the endoplasmic reticulum. This was captured in Biology of Heat Shock Proteins and Molecular Chaperones (Tissières et al. 1994), which, containing chapters on the regulation of hormone signal transduction and the heat shock response by Hsp70 and Hsp90, also established that the heat shock response and molecular chaperones were signatures of heart and brain ischemia and aging. The emphasis of the first edition of Protein Homeostasis (Morimoto et al. 2012) balanced the important mechanistic discoveries on chaperone function and the paths from biogenesis to stable folding and function or to clearance by autophagy and the proteasome. Proteostatic deficiencies in neurodegenerative disease and other diseases of protein conformation that interfere with protein stability and function can be overcome by enhancing the activities of chaperones and restoring the proteasome and autophagy. Whether achieved by genetic approaches or small molecules, it may now be possible to enhance the concentration, conformation, quaternary structure, and/or the location of a protein by readapting the innate biology of the cell to ameliorate the most challenging diseases of our era.

This second edition of Protein Homeostasis provides insights into the physical chemistry of protein polymers and the biochemical and cellular processes for protein quality control that manage folding, stability, and function in each of the subcellular compartments. Several chapters focus on the mechanisms underlying the formation of beneficial amyloids and toxic aggregate structures relevant to neurodegenerative diseases. It has been written for a diverse audience as a comprehensive “state-of-the-art” volume on the breadth of topics that cover the field; it can also serve as the basis for an advanced course in biochemistry, cell biology, or the molecular basis of disease. Consequently, this volume will be invaluable both for advanced researchers and for graduate students and postdoctoral fellows. Moreover, for those entering this field from intersecting disciplines, this volume provides an essential introductory overview.

In putting together this volume, it has been a pleasure to work with so many outstanding colleagues who shared our enthusiasm. Their generosity of time and effort made this book a pleasure to plan and develop. We also appreciate the support and patience of Richard Sever and Barbara Acosta at Cold Spring Harbor Laboratory Press in seeing this project to the end.

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REFERENCES


