Protein Homeostasis

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Front cover artwork: The protein folding landscape. All proteins begin at the top of the folding funnel synthesized as nascent polypeptides with nearly infinite folding possibilities. Intrinsic intramolecular interactions (light blue) partition proteins in the folding landscape through intermediates to the lowest free-energy native state. In vivo, in the cellular environment, these events are strongly determined by interactions with molecular chaperones and other folding catalysts. Competition reactions can lead to intermolecular interactions (medium blue) and the appearance of oligomers, amorphous aggregates, and ordered fibrils.

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Contents

Contents

Preface

The efficient functioning of the proteome is fundamental to all cellular processes, and consequently it is of central importance to the health of the cell and lifespan of the organism. Protein homeostasis, or proteostasis, corresponds to the molecular interactions of each polypeptide within the expressed proteome of each cell and ensures its proper expression, folding, translocation, and clearance. For each protein, this is achieved by a network comprising molecular chaperones, transport machineries, the ubiquitin-dependent proteasome, and autophagic activities that function in concert under optimal conditions to orchestrate proteome health. Stress and aging, however, challenge the proteostasis network to maintain balance, and in certain cases become limiting, thus increasing the risk of cellular pathology and disease.

Although much of the information required for the folding of polypeptide chains into functional three-dimensional native conformations is encoded in the primary sequence, it is clear that the cellular environment controls the stability of the fold and consequently the function of all proteins. Moreover, the folding and stability of the native state is not only challenged by the crowded cellular environment, but it is also strongly influenced by expressed polymorphisms and a myriad of posttranslational modifications that accumulate with age. These contribute to the pool of metastable proteins that readily misfold, aggregate, and in turn amplify the stress of misfolded proteins.

The composition of the proteome, therefore, is a dynamic property of the cell. Proteostasis, however, is regulated both in a cell-autonomous manner to ensure that each cell can achieve an optimal state and by cell-nonautonomous control in metazoans to achieve interdependence among cells and tissues. Collectively, these events, through proteome protective and quality control mechanisms, determine the health of the cell and the lifespan of the organism. Stress represents a prominent challenge to proteostasis that cannot be predicted but for which the cell must be prepared. The challenges incurred during aging—acute stress such as heat shock, oxidants, and metabolic stress or chronic stress when mutant and damaged proteins are expressed—lead to a growing burden of misfolded and damaged proteins.

There is increasing evidence to support the hypothesis that the accumulation of damaged proteins not only has direct consequences on the efficiency and fidelity of cellular processes but, when uncorrected, initiates a cascade of dysfunction, which in humans is associated with a plethora of diseases of protein conformation. These include many of the most challenging diseases to affect us, such as Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), metabolic diseases, and cancer. Although each disease has a distinctive clinical profile with characteristic tissue vulnerability and age-dependent onset, they all have in common the expression of one or more aggregation-prone proteins.

This volume has been written to serve diverse purposes: for an advanced course in cell biology, biochemistry, or the molecular basis of disease or as a comprehensive "state-of-the-art" volume of topics across the breadth of the field. Consequently, this volume will be invaluable for graduate students and postdoctoral fellows, as well as more advanced researchers, and for those entering from intersecting disciplines. Finally, as this volume represents an effort to be comprehensive, the individual chapters should be useful for those looking for a critical assessment of specific domains.

Protein Homeostasis addresses the remarkable story of the life of proteins: from their intrinsic folding properties to the cellular events of synthesis, folding, transport, and clearance and responses to stress, aging, and disease. The topics covered in this volume reflect the current state of the field.

It flows seamlessly from the physical biochemistry of protein folding, to protein folding in diverse cells and tissues, to a plethora of diseases of protein conformation, and closes on the development of novel therapeutic strategies.

This story has been told over installments, with each of three previous volumes from Cold Spring Harbor Laboratory Press providing increasing knowledge and new insights into the biology of molecular chaperones, the heat shock and unfolded protein responses, and, more recently, diseases of protein conformation. This volume traces its roots back to *Heat Shock—From Bacteria to Man* (1982), *Stress Proteins in Biology and Medicine* (1990), and *The Biology of Heat Shock Proteins and Molecular Chaperones* (1994). Each book and the chapters therein follow the discoveries that have propelled this field from the initial observations on the heat shock response in *Drosophila* salivary glands and tissue culture cells, the identification of the heat shock proteins and cloning of highly conserved heat shock genes, and the demonstration of the central roles for heat shock factors in transcriptional regulation of the heat shock response to experiments that revealed the remarkable properties and function of the heat shock proteins and molecular chaperones in protein folding and suppression of misfolding.

Emerging from the first Cold Spring Harbor Laboratory meeting in 1982 were the tantalizing hints that the stress response and heat shock proteins could be relevant to human diseases. The molecular chaperone concept was on the horizon but had yet to be supported by experimental evidence. However, it was already clear that the induction of heat shock proteins by a myriad of stress conditions causes a fundamental reprogramming of the cell, leading to a cytoprotective state that provides not only protection against the same and more extreme stress exposures but also cross-protection against many other forms of environmental and physiological stress. Some 30 years later, the field has flourished, and the stories have become even more compelling. We now understand that the biochemical and biophysical properties of a large family of molecular chaperones that regulate folding, prevent misfolding, and direct damaged proteins to the degradative machinery prevent the accumulation of damaged proteins. This convergence, together with the fundamental understanding that protein damage has serious consequences to the cell, is further amplified with the growing appreciation that aging represents a significant risk factor for proteome stability.

An emphasis of this new volume is the evidence that proteostatic deficiencies in neurodegenerative disease and other diseases of protein conformation that interfere with protein stability and function can be suppressed 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 reach the goal of enhancing the concentration, conformation, quaternary structure, and/or location of a protein by readapting the innate biology of the cell to ameliorate the most challenging diseases of our era.

Finally, we would like to thank our colleagues whose inspiration and generosity made this book a pleasure to plan and develop. The editors thank Richard Sever and Barbara Acosta at Cold Spring Harbor Laboratory Press for their encouragement, support, and patience in seeing this project to the end.

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