Heat Shock Proteins

Volume 11

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Heat Shock Proteins: key mediators of Health and Disease. Heat shock proteins (HSP) are essential molecules conserved through cellular evolution required for cells to survive the stresses encountered in the environment and in the tissues of the developing and aging organism. These proteins play the essential roles in stress of preventing the initiation of programmed cell death and repairing damage to the proteome permitting resumption of normal metabolism. Loss of the HSP is lethal either in the short-term in cases of acute stress or in the long-term when exposure to stress is chronic. Cells appear to walk a fine line in terms of HSP expression. If expression falls below a certain level, cells become sensitive to oxidative damage that influences aging and protein aggregation disease. If HSP levels rise above the normal range, inflammatory and oncogenic changes occur. It is becoming clear that HSP are emerging as remarkably versatile mediators of health and disease. The aim of this series of volumes is to examine how HSP regulation and expression become altered in pathological states and how this may be remedied by pharmacological and other interventions.

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Prokaryotic Chaperonins

Multiple Copies and Multitude Functions

Springer

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Preface

Chaperonins are a fascinating class of molecular chaperones that form a double toroidal architecture, consisting of two isologous rings of 7–9 subunits, each with a large central cavity for binding and encapsulation of naïve or unfolded substrate proteins. Chaperonin-bound substrates are encapsulated with the help of the co-chaperonin that acts as a lid for the central cavity. The bound substrates are allowed to fold upon encapsulation in an ATP-dependent manner. This enables sequestering the substrates from adverse folding environment and consequently facilitates their folding. Physiological function and mechanism of action of the chaperonins have been well-studied using *Escherichia coli* chaperonin, GroEL, as the model. The biological significance of chaperonins stems from the fact that they assist folding of about 10–15% of cellular proteins, including many essential proteins. A plethora of information through structural and functional studies on GroEL has enabled the proposition of a generalized mechanism of action and regulation of prokaryotic chaperonins.

However, the discovery of multiple chaperonins with a multitude of functions, in about 30% of the newly sequenced bacteria, has dramatically shifted the paradigm of chaperonin function. The presence of multiple chaperonins introduced new conundrums on whether they enhance general chaperoning ability in the cell or have deviated to undertake any specific novel cellular roles. Although the latter view is widely supported, evidence for the former is beginning to appear. While some of these multiple-copy chaperonins can functionally replace *E. coli* GroEL and thus are essential, the others are ineffective and likewise are non-essential. Surprisingly, several of these non-essential paralogues have been demonstrated to have acquired novel moonlighting functions, including antigenic and pathogenic functions. Notably, the GroEL1 in mycobacteria has been implicated in the formation of granulomas and disease progression, while GroEL2 acts as a general chaperone. Furthermore, in different classes of bacteria such as myxobacteria, cyanobacteria and rhizobia, the chaperonins have exhibited life-phase specific functional regulation. These observations directly imply functional variation amongst these chaperonin paralogues.

Therefore, the *extra* copies of chaperonins in several bacteria are believed to assist the organism during different phases of its life cycle. Furthermore, studies on the phylogenetic distribution of multiple GroELs revealed a specific pattern of distribution, rather than a random distribution, suggesting a strong biological correlation for the presence of multiple genes. Moreover, evolutionary analysis suggested that acquisition of multiple chaperonins followed case-specific evolutionary paths. For example, while multiple copies of the chaperonins resulted from a gene-duplication event in mycobacteria, in methanogens they resulted from horizontal acquisition. Therefore, in a nutshell, with multitude functions and diverse biological roles, these multiple chaperonins are changing the outlook of chaperonin biology. These studies, therefore, have suggested larger functional roles for chaperonins and consequently necessitated a comprehensive understanding of the structural, biochemical, functional and phylogenetic attributes of this class of molecular chaperones. Gaining evidences of the diverse roles of chaperonins would enable translating the biological significance of the multiple copies towards human welfare. Therefore, in this book, we present the current perception on the multiple chaperonins and their physiological and functional specificities.

Since the book deals with chaperonins, proteins that assist folding of other proteins in the cell, we have begun the book with an introductory note on the current advances in the understanding of structure-function relations and mechanism of action of chaperonins in Chap. 1. In addition, a brief sketch on the classification of the chaperonins into Group I, Group II and newly identified Group III, with an emphasis on their physiological features, has also been discussed in this chapter. Since different chaperonin genes are regulated differently, Chap. 2 has been devoted to review classical and novel modes of regulation of heat shock response in different bacteria. Moving on to the multiple chaperonins, Chap. 3 presents an overview on the functional diversity of multiple chaperonins in prokaryotes and will introduce subsequent chapters, 4 through 9, each of which comprehensively reviews different fascinating cases of multiple chaperonins. To understand how these multiple chaperonin genes have emerged, evolution and phylogenetic distribution of the multiple chaperonins are presented in Chap. 10. This chapter, with interesting activities for the readers, discusses possible modes of evolution and pathways of distribution of multiple chaperonins.

Therefore, we are convinced that this book, by bringing together leading experts in the field of chaperone biology, presents enthusiastic readers with a comprehensive review on the current advances in the understanding of the functional diversity of chaperonins, particularly multiple chaperonins. This is followed by an exciting and novel discussion on the possible modes of evolution and distribution of these multiple chaperonins. Therefore, we believe this book will serve as a reference for life science researchers, particularly those in the field of protein folding and molecular chaperones. Santosh is Newton International Fellow at the University of Birmingham, UK, sponsored by the The Royal Society, The British Academy and the Academy of Medical Sciences, UK. Further, we wish to acknowledge the support of Department of Biotechnology, India.

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About the Editors

C. M. Santosh Kumar started his research career as a molecular geneticist, understanding the functions of molecular chaperones in health and disease. His research aimed at understanding the functions of the bacterial chaperonins, especially that of the multiple chaperonins. He has demonstrated that the activity of a mycobacterial chaperonin is regulated by a phosphorylation switch that facilitates oligomerization. His current interests include unravelling the role of mycobacterial chaperonins in the establishment and progression of tubercular diseases.

Shekhar C. Mande is a structural biologist interested in understanding the molecular attributes of mycobacterial stress proteins. He started his career as a structural biologist in understanding the structural features of peanut lectin. Further, he became interested in the structure-function relations of mycobacterial stress proteins, such as the redox proteins and heat shock proteins. He led the way towards the understanding of structural features of the mycobacterial chaperonin proteins. His work demonstrated that mycobacterial chaperonins exhibit noncanonical attributes that are evolved to assist the pathogen in its disease establishment and progression. Concurrently, he began to explore the system-wide functional interactions amongst the mycobacterial proteins. These investigations have led to the identification of several novel interactions that are currently being examined.