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The Chaperonopathies
Diseases with Defective Molecular Chaperones

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The Chaperonopathies

Diseases with Defective Molecular Chaperones

An Introduction and Guide to Diseases in which Chaperones Play an Etiologic-Pathogenic Role

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This book is dedicated to medical researchers and practitioners, clinicians and pathologists across all specialties. We hope that the book will help them in the planning of clinical–pathologic investigations on chaperonopathies, and also in dealing with patients and in managing a group of diseases generally ignored until now

Preface

This book is about a number of pathological conditions, the chaperonopathies, which probably existed since remote times and have been studied for years but were grouped together in a coherent nosological category only recently.

The book is intended to be an introduction to the chaperonopathies for researchers and also for practitioners in clinical medicine and pathology. It was conceived as a guide for future research. In this regard, it opens a quarry for mining. It provides the basic information, including references to learn about chaperonopathies from those that described them originally, so research projects can be prepared and launched.

The subject matter includes chaperones with demonstrated chaperoning roles and other molecules related to them evolutionarily and/or functionally. It focuses on conditions with chaperone malfunction and associated pathologies. In this regard it is important to point out that chaperones have typical chaperoning functions pertaining to protein homeostasis (i.e., assisting in protein folding, protection from aggregation, refolding, translocation, degradation, dissolution of protein aggregates, and selective autophagy) and, in many instances, other functions more or less unrelated to the typical ones. For example, Hsp60 participates in protein folding inside mitochondria but it has, in addition, other diverse functions such as interaction with components of the innate immune system, resulting in cytokine production. The book includes examples of chaperonopathies in which the typical chaperoning functions are compromised as well as examples of conditions in which the noncanonical roles of chaperones are affected. Thus, the book centers on the chaperone molecules, which if abnormal, can cause chaperonopathies, with manifestations on protein homeostasis and/or beyond.

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Prologue

The accumulation of misfolded proteins may be most familiar to those who understand the role of protein aggregates in the pathophysiology of neurodegenerative disorders (e.g., Alzheimer's disease). The pathophysiology of these conditions is complex as the accumulation of protein aggregates not only depends on the cell's ability to prevent protein misfolding, but also on the cell's ability to degrade these proteins by the ubiquitin proteasome system and/or autophagic machineries. Chaperones (also called heat shock proteins although not all of these are chaperones and, vice versa, not all chaperones are heat shock proteins) play a critical role not only in protein folding, but also in the degradation and autophagic removal of misfolded proteins. When chaperone activity is impaired, protein aggregates, or any of the preceding protein intermediaries, can induce cell death—a process called proteotoxicity—which is one mechanism that underlies the pathophysiology of neurodegenerative diseases. Studies aiming at elucidating the role of proteotoxicity in neurodegenerative diseases have led to the discovery that increasing heat shock protein expression can improve cognitive function in preclinical models. Increased heat shock protein expression also has the beneficial side effects of augmenting the solubility of misfolded protein aggregates and enhancing degradation of the latter, experimentally. This is a significant finding since therapies exist today that induce heat shock proteins, including exercise and specific FDA (Food and Drug Administration) approved drugs, which are able to lower the burden of misfolded polypeptides and attenuate pathological progression. Experimentally, these therapies have proven quite successful in clinical scenarios where few options are available.

The importance of chaperones does not end with these well-known neurodegenerative conditions, including Alzheimer's, Parkinson's, Huntington's, and prion diseases. Chaperones also play a predominant role in a growing number of very common pathologies, including cystic fibrosis and heart failure. For example, the most common mutation causing cystic fibrosis encodes a misfolded protein that is preferentially degraded by the ubiquitin proteasome system, resulting in a lack of the protein on the cell's surface. Small molecule compounds that correct this mutant CFTR-protein misfolding have been developed to prevent its degradation and show promise in pre-clinical and preliminary clinical studies. And the list of diseases that have misfolded proteins and their associated

"proteotoxicity" underlying their pathogenesis continues to grow. Not only have misfolded proteins been identified in heart failure patients, but it has also been demonstrated that cardiac expression of misfolded oligomers alone can be responsible for the observed heart failure. It is predicted that therapies that can prevent protein misfolding in heart failure patients, including promoting an increase in chaperone expression, may offer therapies so desperately needed for this most common cause of death in the United States.

Our understanding of protein quality control and the role of molecular chaperones in the pathophysiology of many human diseases, as discussed in this book, is just beginning and represents a common theme that may make advances in one field applicable to many others. By understanding the common pathophysiology of diseases based on their relationship to chaperones allows similar conditions to be studied together, systematically, for the first time in a coherent matrix. The material presented in this book represents an outstanding foundation of knowledge for both physicians and scientists in clinical practice and translational research in their quest to develop novel therapies, diagnostics, and appropriate differential diagnoses for human illnesses due to abnormal chaperones (i.e., the chaperonopathies). It is hoped that by elucidating these maladies as a significant group of important pathological conditions, many of them serious and widespread, the larger medical community will be more aware of the importance of the field and give it the attention it largely lacks at present.

November 2012

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Chapter 1
Overview and Book Plan

Abstract This chapter provides an introduction to the biology and pathology of molecular chaperones, many of which are heat-shock proteins, involved in protein homeostasis and other unrelated functions. When chaperones are defective structurally and/or functionally they may cause disease. These diseases in which chaperones play an etiologic-pathogenic role are the chaperonopathies. The chapter also gives a clinical-pathological overview of chaperonopathies and guidelines for their identification and diagnosis. It briefly describes how to detect and characterize a chaperonopathy in a patient. Chaperones can be useful biomarkers for disease diagnosis and monitoring, including evaluation of prognosis and response to treatment. This and the potential of chaperones for therapy, i.e., chaperonotherapy, are aspects of chaperonology also outlined in the chapter.

Keywords Heat shock protein · Molecular chaperone · Protein homeostasis · Abnormal chaperones · Chaperonopathies · Molecular chaperone disorders · Pathological chaperones · Hsp diseases · Abnormal Hsp · Hsp pathology · Hsp biomarkers

1.1 Hsp and Molecular Chaperones

A heat-shock protein (Hsp) is, strictly speaking, the product of a gene inducible by a sudden and short-lasting temperature elevation, i.e., heat shock. However, the term Hsp is used with great flexibility to indicate proteins that are the product of genes that can respond to a variety of stressors, not just heat shock. Many Hsp have chaperoning ability, in the sense that they assist nascent polypeptides to fold correctly. Other canonical functions of chaperones include, in addition to protein folding, assisting protein refolding and translocation through membranes, ushering proteins damaged beyond repair to degradation, and dissolution of protein aggregates. One may add selective autophagy. In summary, the canonical functions of chaperones pertain to protein quality control, essentially the maintenance of protein homeostasis. In addition, chaperones have other function unrelated to protein homeostasis, as it will be explained later.

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