

PREFACE

Folding is essential to achieve the appropriate structure and function for all proteins. Despite the exquisite cellular mechanisms regulating and assisting protein folding, there are instances where accumulation of misfolded proteins occurs in different tissues, causing cell death and tissue degeneration. Protein misfolding is now viewed as an intrinsic feature of protein-folding reactions, constantly challenging the cellular environment. The goal of the book is to provide students, basic scientists, and medical professionals with an opportunity to learn about the basic principles of protein misfolding diseases as well as the current and emerging therapies being developed. Among protein misfolding diseases, the amyloid diseases are the most common and are more widely studied. There are currently 26 amyloid diseases described in the literature affecting different tissues and with diverse symptoms. Each disease is characterized by the amyloid deposition of different protein precursors. Some of these amyloid diseases are rare, whereas other conditions, such as Alzheimer disease, are very common and are considered a serious health care concern for the aging population. These diseases are generally incurable, although the various therapeutic strategies presented in this book help to slow the progression of disease.

Protein misfolding is the process in which proteins fail to adopt and maintain their folded conformation through a number of intrinsic and extrinsic mechanisms. As a result, partially folded intermediates start being populated, triggering an aggregation process that causes both loss and gain of function. In this book we offer a broad integrated overview of the process of protein misfolding, with chapters written by expert basic scientists and protein misfolding clinicians. We start by reviewing the basis of protein misfolding, the protein folding process *in vivo*, with an overview of the various model systems currently in use, spanning from the eukaryotic *Saccharomyces cerevisiae*, the nematode *Caenorhabditis elegans*, and the fruit fly *Drosophila melanogaster*, all the way to mammalian systems such as mouse models.

We describe in detail selected examples of protein misfolding diseases that are characterized by a gain of function, where toxic intermediates and/or

amyloid fibrils cause cell damage and tissue degeneration, including diseases affecting the central nervous system, such as Alzheimer disease, spongiform encephalopathies, amyotrophic lateral sclerosis (ALS), and Huntington disease. We have included an overview of systemic amyloid diseases with a special chapter for dialysis-related amyloidosis.

We also review a wide variety of loss-of-function protein misfolding diseases, including cystic fibrosis, cataracts, type 2 diabetes, lysosomal storage diseases, and a new category of protein misfolding diseases caused by nonsynonymous single-nucleotide polymorphisms (nsSNPs) in enzymes, such as thiopurine methyltransferase, responsible for the processing of chemotherapeutic agents.

It is known that there are number of accessory molecules and risk factors that affect protein misfolding diseases, and we have explored the role of metals, glycosaminoglycans, serum amyloid P component, membranes, and oxidative stress. A special chapter is devoted to the role of aging in aggregation-mediated proteotoxicity.

We offer a complementary clinical view of protein misfolding diseases in the second part of the book, starting with an overview about diagnosis of protein misfolding diseases. Diagnosis of protein misfolding diseases is not simple. We have reviewed the various approaches followed to make an accurate diagnosis, including imaging, biomarker discovery, and a panel of clinical evaluations and tests.

We conclude the book by offering an excellent overview of the therapies currently used in a number of the protein misfolding maladies and the emerging therapeutic strategies that are now being tested for a number of protein misfolding disorders and that can easily be applied for many related diseases.

This book is the result of the hard work and efforts of many talented scientific colleagues who generously agreed to contribute to this book. I hope that their knowledge and analysis of the issues related to protein misfolding diseases may inspire your future research and medical endeavors.

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