

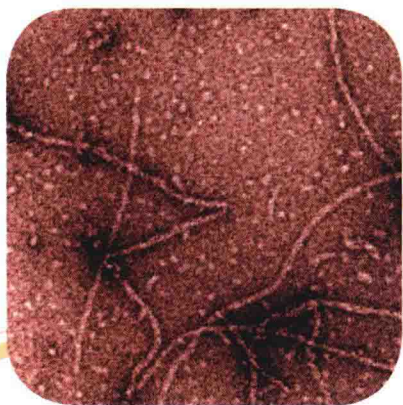
The background of the cover features a dark, reddish-brown microscopic image of neural tissue, showing complex branching patterns. Overlaid on this are several thin, flowing yellow lines that create a sense of movement and connect different parts of the cover.

Protein Folding Disorders of the Central Nervous System

Editors

Jorge Ghiso

Agueda Rostagno



Protein Folding Disorders of the Central Nervous System

This exciting new book explores the dark side of the molecular protein assembly bringing an updated view of how failures in the homeostatic mechanisms that efficiently regulate protein folding leads to the accumulation of structurally abnormal pathogenic assemblies, encompassing an emerging group of diseases collectively known as "Protein Folding Disorders." This complex and diverse group of chronic and progressive entities are bridged together by their relationship to structural transitions in the native state of specific proteinaceous components, which for reasons poorly understood, convert into polymeric aggregates that generate poorly soluble tissue deposits and which are considered today the culprit of the disease pathogenesis in their respective diseases. Despite the diversity in the amino acid sequence of the different proteins involved in these heterogeneous disorders, all the pathologic conformers can trigger cascades of events ultimately resulting in cell dysfunction and death with devastating clinical consequences in many of the most precious aspects of human existence including personality, cognition, memory, and skilled movements.

World Scientific
www.worldscientific.com
10517 hc

ISBN 978-981-3222-95-3



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NEW JERSEY • LONDON • SINGAPORE • BEIJING • SHANGHAI • HONG KONG • TAIPEI • CHENNAI • TOKYO

Published by

World Scientific Publishing Co. Pte. Ltd.

5 Toh Tuck Link, Singapore 596224

USA office: 27 Warren Street, Suite 401-402, Hackensack, NJ 07601

UK office: 57 Shelton Street, Covent Garden, London WC2H 9HE

Library of Congress Cataloging-in-Publication Data

Names: Ghiso, Jorge, editor. | Rostagno, Agueda, editor.

Title: Protein folding disorders of the central nervous system / edited by

Jorge Ghiso (New York University, USA), Agueda Rostagno (New York University, USA)

Description: New Jersey : World Scientific, 2017. | Includes bibliographical references.

Identifiers: LCCN 2017011131 | ISBN 9789813222953 (hc : alk. paper)

Subjects: | MESH: Central Nervous System Diseases--etiology | Proteostasis Deficiencies--complications | Proteostasis Deficiencies--physiopathology

Classification: LCC RA644.P93 | NLM WL 301 | DDC 616.8/3--dc23

LC record available at <https://lccn.loc.gov/2017011131>

British Library Cataloguing-in-Publication Data

A catalogue record for this book is available from the British Library.

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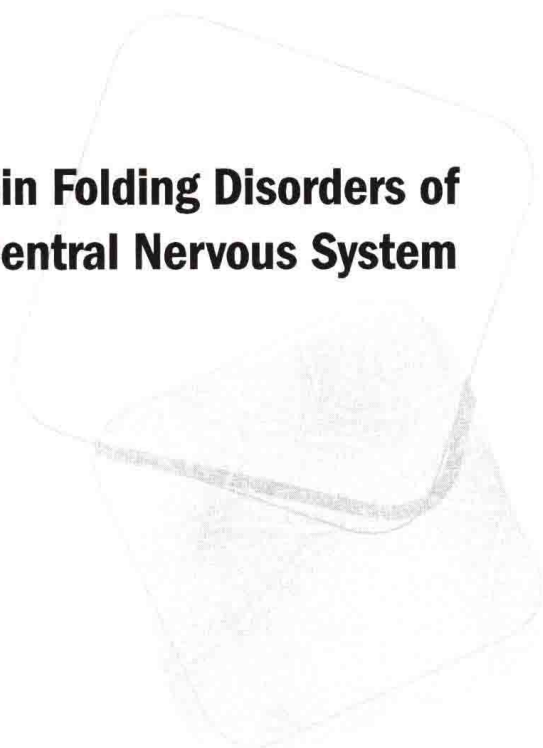
Desk Editors: Kalpana Bharanikumar/T. Yugarani

Typeset by Stallion Press

Email: enquiries@stallionpress.com

Printed in Singapore

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Preface

The proteins of a living organism, after synthesis at the ribosome, must properly fold into specific conformational states to successfully perform their biological function. To this aim, all cells possess complex mechanisms to efficiently regulate protein assembly into functionally active and optimally balanced states. In spite of these homeostatic mechanisms set in place, under some conditions, proteins fail to fold correctly, or to remain correctly folded in living systems, a failure that eventually leads to the accumulation of structurally abnormal pathogenic assemblies. The term “protein misfolding disorders” refers to an emerging complex group of chronic and progressive entities in which the pathogenesis of the respective diseases is driven by structural transitions in the native state of specific proteinaceous components into polymeric aggregates which generate poorly soluble tissue deposits.

Here, we took the challenge to organize a book focusing on diseases associated with protein misfolding in the central nervous system (CNS), which we felt needed to be addressed given the growing number of reports linking abnormal protein folding/aggregation to human disease, in general, and neurodegeneration, in particular. Although distinguished by disease-specific pathology and clinical presentations, these disorders share conspicuous similarities. They are mostly of sporadic origin and, since they are largely age-related, their relevance continues to rise as the number of individuals affected by these conformational disorders is expected to

increase as the world population ages. Current therapeutic strategies are only aimed at alleviating symptoms, and in most cases the normal physiological function of the proteins that aggregate in the respective diseases remain unknown. These proteins are, however, all intimately associated with the specific disorders, as mutations in the gene encoding the disease-linked protein, or its precursor, cause early-onset familial disease.

The book is divided into 14 chapters that provide a comprehensive, state-of-the-art perspective of the topic under discussion, bringing insights into the biological/biophysical mechanisms of protein folding and their relationship to CNS diseases linked to aberrant protein conformations. Individual chapters are dedicated to the most common neurodegenerative diseases associated with protein aggregation/fibrillization, focusing on the nature of the pathogenic species and the pathways involved in Alzheimer's, Parkinson's, and Huntington diseases as well as in amyotrophic lateral sclerosis, and prion diseases. A group of contributions is focused on the intracellular pathways and organelles affected by the different disease conditions and the transmissibility of protein misfolding, whereas another set of chapters is dedicated to novel strategies to therapy for these devastating diseases.

The combination of contributions compiled in this volume is expected to be of interest to the large audience of protein chemists, biochemists, and biophysicists from postgraduate level onward, as well as to clinicians, and all scientists with broad interests in aspects relating to structural biology, protein folding, and disease, as well as in the molecular and cellular aspects of disease pathogenesis in the CNS. We hope that this overview on this key biological problem will make this volume a resourceful source of information that bridges together different aspects of these complex problem.

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Contents

<i>Preface</i>	v
<i>List of Contributors</i>	vii
<i>List of Figures</i>	xv
<i>List of Tables</i>	xix
Chapter 1 Misfolding, Aggregation, and Amyloid Formation: The Dark Side of Proteins	1
<i>Agueda Rostagno and Jorge A. Ghiso</i>	
Chapter 2 Oligomers at the Synapse: Synaptic Dysfunction and Neurodegeneration	33
<i>Emily Vogler, Matthew Mahavongtrakul, and Jorge Busciglio</i>	
Chapter 3 Prion-like Protein Seeding and the Pathobiology of Alzheimer's Disease	57
<i>Lary C. Walker</i>	
Chapter 4 The Tau Misfolding Pathway to Dementia	83
<i>Alejandra D. Alonso, Leah S. Cohen, and Viktoriya Morozova</i>	

Chapter 5	The Biology and Pathobiology of α -Synuclein <i>Joel C. Watts, Anurag Tandon, and Paul E. Fraser</i>	109
Chapter 6	Impact of Loss of Proteostasis on Central Nervous System Disorders <i>Sentiljana Gumeni, Eleni N. Tsakiri, Christina-Maria Cheimonidi, Zoi Evangelakou, Despoina Gianniou, Kostantinos Tallas, Eleni-Dimitra Papanagnou, Aimilia D. Sklirou, and Ioannis P. Trougkos</i>	131
Chapter 7	Protein Misfolding and Mitochondrial Dysfunction in Amyotrophic Lateral Sclerosis <i>Giovanni Manfredi and Hibiki Kawamata</i>	163
Chapter 8	Impact of Mitostasis and the Role of the Anti-oxidant Responses on Central Nervous System Disorders <i>Sentiljana Gumeni, Eleni N. Tsakiri, Christina-Maria Cheimonidi, Zoi Evangelakou, Despoina Gianniou, Kostantinos Tallas, Eleni-Dimitra Papanagnou, Aimilia D. Sklirou, and Ioannis P. Trougkos</i>	185
Chapter 9	Propagation of Misfolded Proteins in Neurodegeneration: Insights and Cautions from the Study of Prion Disease Prototypes <i>Robert C. C. Mercer, Nathalie Daude, and David Westaway</i>	203
Chapter 10	Endoplasmic Reticulum Stress Response in Neurodegenerative Diseases <i>Hyung Don Ryoo</i>	225
Chapter 11	Proteomic Analysis of Huntingtin-Associated Proteins Provides Clues to Altered Cell Homeostasis in Huntington's Disease <i>Naoko Tanese</i>	239

Chapter 12	Overcoming the Obstacle of the Blood–Brain Barrier for Delivery of Alzheimer’s Disease Therapeutics <i>Eliezer Masliah and Brian Spencer</i>	249
Chapter 13	Immunotherapies for Alzheimer’s Disease <i>Einar M. Sigurdsson</i>	267
Chapter 14	Role of the Microbiome in Polyphenol Metabolite-Mediated Attenuation of β -amyloid and tau Protein Misfolding in Alzheimer’s Disease <i>Jun Wang, Lap Ho, Jeremiah Faith, Kenjiro Ono, Hanna Księżak-Reding, Ali Sharma, Breanna Valcarcel, and Giulio M. Pasinetti</i>	281
	<i>Index</i>	305

List of Figures

Figure 1.1	Misfolded protein deposits in AD.	4
Figure 1.2	Schematic representation of the A β misfolded pathway resulting in oligomerization and amyloid fibril formation.	9
Figure 2.1	Summary of oligomeric proteins and associated diseases.	35
Figure 3.1	Neuropathological lesions in AD.	58
Figure 3.2	Neuropathological features in spongiform encephalopathies.	65
Figure 4.1	Cartoon of Pathological Human tau (PH-Tau).	85
Figure 4.2	A hypothetical scheme of the phosphorylation-induced self-assembly of wild-type and FTDP-17 mutated tau proteins.	94
Figure 4.3	Proposed mechanisms of neurodegeneration.	100
Figure 5.1	PD pathology and α -syn fibril formation.	110
Figure 5.2	A schematic representation of α -syn indicating its three predominant domains.	111

Figure 6.1	Schematic depiction of the main PN components' functional implication in the maintenance of neuron homeodynamics.	150
Figure 8.1	Mitochondria dynamics.	187
Figure 8.2	Nrf2/Keap1 anti-oxidant response signaling pathway in neurons.	194
Figure 9.1	Neuropathological features of prion disease.	204
Figure 9.2	Domain structure of PrP and prion-related concepts.	206
Figure 10.1	IRE1 pathway.	226
Figure 10.2	PERK/ATF4 pathway.	228
Figure 11.1	Diagram illustrating the association of <i>HTT</i> with RNA transport.	242
Figure 12.1	Schematic processing of APP.	250
Figure 12.2	Diagram of the BBB.	252
Figure 12.3	Diagram of the BBB transport mechanisms.	253
Figure 13.1	Clearance and prevention of spread of pathological A β peptide and tau protein by antibodies.	270
Figure 14.1	Representative structures of polyphenols from grape and grape-derived products.	283
Figure 14.2	Composition of GSPE and models of interaction with A β 40.	286
Figure 14.3	GSPE and aberrant tau aggregation.	288
Figure 14.4	Select brain-penetrating polyphenolic metabolites from GSPE and CGJ are bioactive in preventing acute oA β -induced LTP impairment through CREB signaling.	290
Figure 14.5	GDP and synaptic plasticity.	293